Mobile phase: *concentrated ammonia R, toluene R, dioxan R* (1:40:60 *V/V/V*).

Application: 5 µL.

Development: over a path of 15 cm.

Drying: in a current of air for 15 min.

Detection: expose to iodine vapour for 30 min.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

E. About 1 mg gives the reaction of nitrates (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

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). Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *sertaconazole nitrate CRS* and 5.0 mg of *miconazole nitrate CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;

– *stationary phase*: *nitrile silica gel for chromatography R1* (10 µm).

Mobile phase: *acetonitrile R1*, 1.5 g/L solution of *sodium dihydrogen phosphate R* (37:63 *V/V*).

Flow rate: 1.6 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 20 µL.

Run time: 1.3 times the retention time of sertaconazole.

Retention time: nitrate ion = about 1 min; miconazole = about 17 min; sertaconazole = about 19 min.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to miconazole and sertaconazole.

Limits:

– *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to the nitrate ion.

Water (*2.5.12*): maximum 1.0 per cent, determined on 0.50 g.

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

ASSAY

Dissolve 0.400 g in 50 mL of a mixture of equal volumes of *anhydrous acetic acid R* and *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

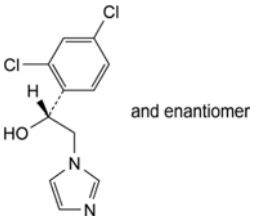
1 mL of *0.1 M perchloric acid* is equivalent to 50.08 mg of $C_{20}H_{16}Cl_3N_3O_4S$.

STORAGE

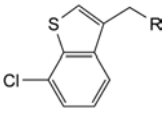
Protected from light.

IMPURITIES

Specified impurities: *A, B, C.*



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



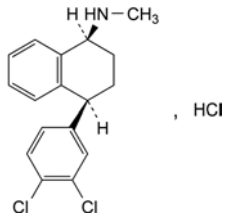
B. R = Br: 3-(bromomethyl)-7-chloro-1-benzothiophen,

C. R = OH: (7-chloro-1-benzothiophen-3-yl)methanol.

01/2011:1705

SERTRALINE HYDROCHLORIDE

Sertralini hydrochloridum



$C_{17}H_{18}Cl_3N$ M_r 342.7

[79559-97-0]

DEFINITION

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, slightly soluble in acetone and in 2-propanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Carry out either tests A, B, C or tests B, C, D.

A. Specific optical rotation (*2.2.7*): + 38.8 to + 43.0 (anhydrous substance), measured at 25 °C.

Solvent mixture. Dilute 1 volume of a 103 g/L solution of *hydrochloric acid R* to 20 volumes with *methanol R*.

Dissolve 0.250 g in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *sertraline hydrochloride CRS*.

If the spectra obtained in the solid state show differences, record new spectra using 10 g/L solutions in *methylene chloride R*.

C. Dissolve 10 mg in 5 mL of *anhydrous ethanol R* and add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

D. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity. Liquid chromatography (*2.2.29*).

Solvent mixture: *diethylamine R, hexane R, 2-propanol R* (1:40:60 *V/V/V*).

Test solution. Dissolve 60.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a). Dissolve the contents of a vial of *sertraline for system suitability CRS* (containing impurity G) in 1.0 mL of the solvent mixture.

Reference solution (b). Dilute 0.5 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *silica gel AD for chiral separation R* (5 µm).

Mobile phase: mix 30 volumes of *hexane R* and 70 volumes of a mixture of 1 volume of *diethylamine R*, 25 volumes of *2-propanol R* and 975 volumes of *hexane R*.

Flow rate: 0.4 mL/min.

Detection: spectrophotometer at 275 nm.

Injection: 20 µL.

Run time: 30 min.

Elution order: sertraline, impurity G.

System suitability:

- *resolution*: minimum 1.5 between the peaks due to sertraline and impurity G in the chromatogram obtained with reference solution (a);
- *signal-to-noise ratio*: minimum 10 for the peak due to sertraline in the chromatogram obtained with reference solution (b).

Limit:

- *impurity G*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent).

Impurity E. Liquid chromatography (*2.2.29*).

Solvent mixture: mobile phase A, mobile phase B (50:50 *V/V*).

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

Reference solution (a). Dissolve 5.0 mg of *mandelic acid CRS* (impurity E) in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *benzoic acid R* and 20 mg of *mandelic acid R* (impurity E) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

- *mobile phase A*: dissolve 1.0 g of *sodium laurilsulfate R* in 800 mL of *water R* and add 200 mL of *acetonitrile R1*; add 1.0 mL of *phosphoric acid R* and mix;
- *mobile phase B*: dissolve 1.0 g of *sodium laurilsulfate R* in 100 mL of *water R* and add 900 mL of *acetonitrile R1*; add 1.0 mL of *phosphoric acid R* and mix;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	60	40
8 - 9	60 → 10	40 → 90
9 - 16	10	90

Flow rate: 1 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Relative retention with reference to sertraline (retention time = about 18 min): impurity E = about 0.2; benzoic acid = about 0.3.

System suitability: reference solution (b):

- *resolution*: minimum 5.0 between the peaks due to impurity E and benzoic acid.

Limit:

- *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Introduce 0.250 g of the substance to be examined into a 15 mL stoppered centrifuge tube, add 2.0 mL of *methanol R* and 0.20 mL of a 25 per cent solution of *potassium carbonate R* and mix in a vortex mixer for 30 s. Add 8.0 mL of *methylene chloride R*, stopper the tube and mix in a vortex mixer for 60 s. Add 1 g of *anhydrous sodium sulfate R*, mix well and then centrifuge for about 5 min.

Reference solution (a). Dissolve the contents of a vial of *sertraline for peak identification CRS* (containing impurities A, B, C and F) in 0.2 mL of *methylene chloride R*.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 20.0 mL with *methylene chloride R*.

Column:

- *material*: fused silica;
- *size*: *l* = 30 m, Ø = 0.53 mm;
- *stationary phase*: *polymethylphenylsiloxane R* (film thickness 1.0 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 9 mL/min.

Split ratio: 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	200
	1 - 31	200 → 260
	31 - 39	260
Injection port		250
Detector		280

Detection: flame ionisation.

Injection: 1 µL.

Identification of impurities: use the chromatogram supplied with *sertraline for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and F.

Relative retention with reference to sertraline (retention time = about 24 min): impurity B = about 0.5; impurities C and D = about 0.7; impurity A = about 1.05; impurity F = about 1.1.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to sertraline.

Limits:

– *impurities A, B, F*: for each impurity, maximum 0.2 per cent;

– *sum of impurities C and D*: maximum 0.8 per cent;

– *unspecified impurities*: for each impurity, maximum 0.10 per cent;

– *total*: maximum 1.5 per cent;

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

Heavy metals (*2.4.8*): maximum 20 ppm.

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 20.0 mL with the same solvent. 12 mL of the solution complies with test B. Prepare the reference solution using lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with *ethanol (96 per cent) R*.

Water (*2.5.12*): maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution. To 28.6 mL of *glacial acetic acid R* slowly add, while stirring and cooling, 34.8 mL of *triethylamine R*, and dilute to 100 mL with *water R*. Dilute 10 mL of this solution to 1000 mL with *water R*.

Test solution. Dissolve 55.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution. Dissolve 55.0 mg of *sertraline hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (4 µm);

– *temperature*: 30 °C.

Mobile phase: *methanol R*, buffer solution, *acetonitrile R* (15:40:45 *V/V/V*).

Flow rate: 1.8 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: twice the retention time of sertraline.

Retention time: sertraline = about 1.9 min.

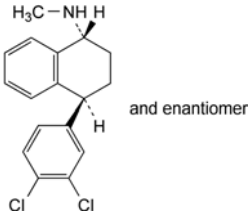
Calculate the percentage content of $C_{17}H_{18}Cl_3N$ from the declared content of *sertraline hydrochloride CRS*.

STORAGE

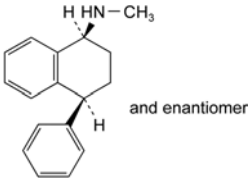
Protected from light.

IMPURITIES

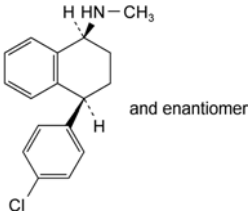
Specified impurities: A, B, C, D, E, F, G.



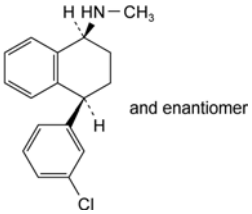
A. (1*RS*,4*SR*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



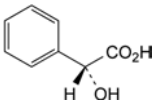
B. (1*RS*,4*RS*)-*N*-methyl-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine,



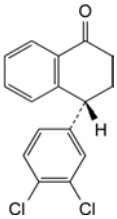
C. (1*RS*,4*RS*)-4-(4-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



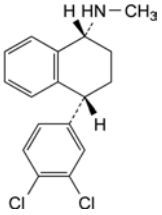
D. (1*RS*,4*RS*)-4-(3-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



E. (2*R*)-hydroxyphenylacetic acid ((*R*)-mandelic acid),



F. (4*R*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one,



G. (1*R*,4*R*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (sertraline enantiomer).