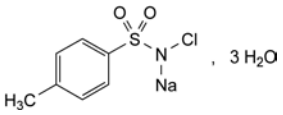
01/2008:0381
corrected 6.0

TOSYLCHLORAMIDE SODIUM

Tosylchloramidum natricum



$C_7H_7ClNNaO_2S,3H_2O$ M_r 281.7

DEFINITION

Sodium *N*-chloro-4-methylbenzene-sulfonimidate trihydrate.

Content: 98.0 per cent to 103.0 per cent of $C_7H_7ClNNaO_2S,3H_2O$.

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

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

IDENTIFICATION

A. Solution S (see Tests) turns *red litmus paper R* blue and then bleaches it.

B. To 10 mL of solution S add 10 mL of *dilute hydrogen peroxide solution R*. A white precipitate is formed which dissolves on heating. Filter the hot solution and allow to cool. White crystals are formed which, when washed and dried at 100-105 °C, melt (*2.2.14*) at 137 °C to 140 °C.

C. Ignite cautiously 1 g, because of the risk of deflagration. Dissolve the residue in 10 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

D. The solution prepared for identification test C gives reaction (a) of sulfates (*2.3.1*).

E. The solution prepared for identification test C gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*): 8.0 to 10.0 for solution S.

Ortho compound. To 2 g add 10 mL of *water R*, mix, add 1 g of *sodium metabisulfite R* and heat to boiling. Cool to 0 °C, filter rapidly and wash with 3 quantities, each of 5 mL, of iced *water R*. The precipitate, dried over *diphosphorus pentoxide R* at a pressure not exceeding 600 Pa, melts (*2.2.14*) at a minimum of 134 °C.

Residue insoluble in anhydrous ethanol: maximum 2 per cent.

Shake 1.00 g with 20 mL of *anhydrous ethanol R* for 30 min, filter on a tared filter, wash any residue with 5 mL of *anhydrous ethanol R* and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

ASSAY

Dissolve 0.125 g in 100 mL of *water R* in a ground-glass-stoppered flask. Add 1 g of *potassium iodide R* and 5 mL of *dilute sulfuric acid R*. Allow to stand for 3 min. Titrate with *0.1 M sodium thiosulfate*, using 1 mL of *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 14.08 mg of $C_7H_7ClNNaO_2S,3H_2O$.

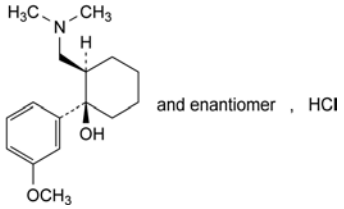
STORAGE

In an airtight container, protected from light.

01/2008:1681
corrected 6.0

TRAMADOL HYDROCHLORIDE

Tramadoli hydrochloridum



$C_{16}H_{26}ClNO_2$ M_r 299.8
[36282-47-0]

DEFINITION

(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in methanol, very slightly soluble in acetone.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 180 °C to 184 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *tramadol hydrochloride CRS*.

C. Chromatograms obtained in the test for impurity E.
Results: the principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *water R* and dilute to 20 mL with the same solvent.

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

Acidity. To 10 mL of solution S, add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M hydrochloric acid*. The solution is red. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Impurity E. Thin-layer chromatography (*2.2.27*).

Test solution (a). Dissolve 0.10 g in *methanol R* and dilute to 2 mL with the same solvent.

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

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

Reference solution (b). Dissolve 5 mg of *tramadol impurity E CRS* in 5 mL of *methanol R*. Dilute 1 mL of the solution to 10 mL with *methanol R*.

Reference solution (c). Dissolve 5 mg of *tramadol impurity A CRS* in 1 mL of reference solution (a).

Plate: *TLC silica gel F_{254} plate R*, prewashed with *methanol R*.

Monographs T-Z

Mobile phase: *concentrated ammonia R, 2-propanol R, toluene R* (1:19:80 *V/V/V*).

Application: 10 µL.

Development: over 2/3 of the plate. Saturate the plate for 20 min with *concentrated ammonia R*. For this, add *concentrated ammonia R* to one trough of a twin trough tank. Just before developing, add the mobile phase to the other trough. Place the plate in the chromatographic tank, ensuring that the layer of silica gel is orientated towards the middle of the tank.

Drying: in air.

Detection: expose the plate to iodine vapour for 1 h, examine in ultraviolet light at 254 nm.

System suitability: the chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

Limit: test solution (a):

– *impurity E*: any spot corresponding to impurity E is not more intense and not greater than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.15 g of the substance to be examined in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (a). Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *tramadol impurity A CRS* in 4.0 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;

– *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: 295 volumes of *acetonitrile R* and 705 volumes of a mixture of 0.2 mL of *trifluoroacetic acid R* and 100 mL of *water R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 270 nm.

Injection: 20 µL.

Run time: 4 times the retention time of tramadol.

Relative retention with reference to tramadol (retention time = about 5 min): impurity A = about 0.85.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurity A and tramadol.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 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 limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

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

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent. 12 mL of this solution complies with test A. Prepare the reference solution using *lead standard solution (2 ppm Pb) R*.

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

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

ASSAY

Dissolve 0.180 g in 25 mL of *anhydrous acetic acid R* and add 10 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 29.98 mg of $C_{16}H_{26}ClNO_2$.

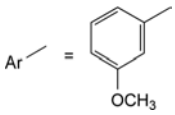
STORAGE

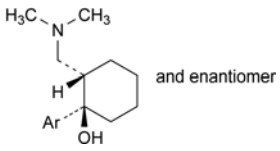
Protected from light.

IMPURITIES

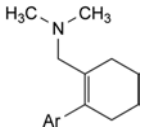
Specified impurities: A, E.

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, D.*

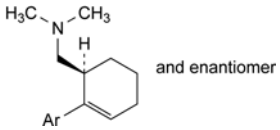




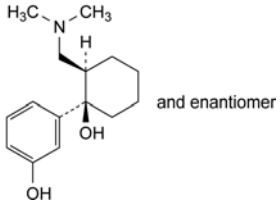
A. (1*RS*,2*SR*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol,



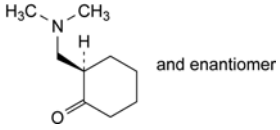
B. [2-(3-methoxyphenyl)cyclohex-1-enyl]-*N*,*N*-dimethylmethanamine,



C. (1*RS*)-[2-(3-methoxyphenyl)cyclohex-2-enyl]-*N*,*N*-dimethylmethanamine,



D. (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-hydroxyphenyl)cyclohexanol,

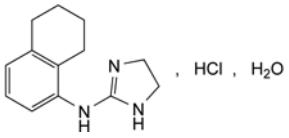


E. (2*RS*)-2-[(dimethylamino)methyl]cyclohexanone.

01/2008:1597

TRAMAZOLINE HYDROCHLORIDE MONOHYDRATE

Tramazolini hydrochloridum monohydricum



$C_{13}H_{18}ClN_3,H_2O$ M_r 269.8
[74195-73-6]

DEFINITION

N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride monohydrate.

Content: 98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *tramazoline hydrochloride monohydrate CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.9 to 6.3 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a). Dissolve 5.0 mg of *tramazoline impurity A CRS* and 5.0 mg of *tramazoline impurity B CRS* in 5 mL of a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and add 5 mL of the test solution.

Reference solution (b). Dilute 0.2 mL of reference solution (a) to 100 mL with a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R*.

Column:
- *size*: *l* = 0.125 m, Ø = 4 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: 2.0 g/L solution of *sodium dodecyl sulfate R* in a mixture of 6 volumes of *2-propanol R*, 42 volumes of *acetonitrile R* and 52 volumes of *water R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 5 µL.

Run time: 3 times the retention time of tramazoline.

Relative retention with reference to tramazoline (retention time = about 6.5 min): impurity A = about 0.71; impurity B = about 0.86.

System suitability: reference solution (a):
- the chromatogram obtained shows 3 clearly separated peaks,
- *resolution*: minimum 1.5 between tramazoline and impurity B.

Limits:
- *impurity A*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *impurity B*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *any other impurity*: not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *sum of other impurities*: not more than twice the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.2 per cent),
- *disregard limit*: 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

Water (*2.5.12*): 6.2 per cent to 7.2 per cent, determined on 0.500 g.

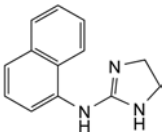
Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

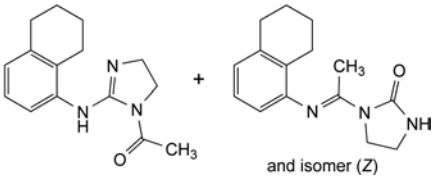
Dissolve 2.000 g in a mixture of 5 mL of *0.1 M hydrochloric acid* and 75 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *1 M sodium hydroxide* is equivalent to 251.8 mg of $C_{13}H_{18}ClN_3$.

IMPURITIES



A. *N*-(naphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine,

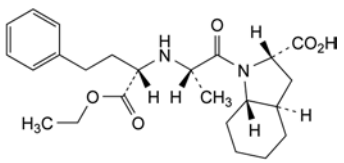


B. mixture of 1-acetyl-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine and 1-[(*EZ*)-1-[(5,6,7,8-tetrahydronaphthalen-1-yl)imino]ethyl]imidazolidin-2-one.

01/2008:2245
corrected 7.0

TRANDOLAPRIL

Trandolaprilum



$C_{24}H_{34}N_2O_5$ M_r 430.5
[87679-37-6]

DEFINITION

(2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

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