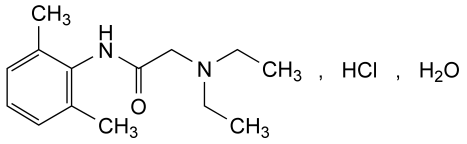
01/2008:0227

LIDOCAINE HYDROCHLORIDE

Lidocaini hydrochloridum



$C_{14}H_{23}ClN_2O,H_2O$ M_r 288.8
[6108-05-0]

DEFINITION

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide hydrochloride monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 74 °C to 79 °C, determined without previous drying.

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

C. To about 5 mg add 0.5 ml of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool and dissolve the residue in 5 ml of *acetone R*. Add 0.2 ml of *alcoholic potassium hydroxide solution R*. A green colour is produced.

D. It gives reaction (a) of chlorides (*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 clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.0 to 5.5.
Dilute 1 ml of solution S to 10 ml with *carbon dioxide-free water R*.

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). Dissolve 50.0 mg of *2,6-dimethylaniline R* (impurity A) in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 10.0 ml of this solution to 100.0 ml with the mobile phase.
Reference solution (b). Dissolve 5 mg of *2-chloro-N-(2,6-dimethylphenyl)acetamide R* (impurity H) in the mobile phase and dilute to 10 ml with the mobile phase.
Reference solution (c). Dilute 1.0 ml of the test solution to 10.0 ml with the mobile phase.
Reference solution (d). Mix 1.0 ml of reference solution (a), 1.0 ml of reference solution (b) and 1.0 ml of reference solution (c) and dilute to 100.0 ml with the mobile phase.
Column:
– *size*: *l* = 0.15 m, Ø = 3.9 mm;
– *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);
– *temperature*: 30 °C.
Mobile phase: mix 30 volumes of *acetonitrile for chromatography R* and 70 volumes of a 4.85 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 8.0 with *strong sodium hydroxide solution R*.
Flow rate: 1.0 ml/min.
Detection: spectrophotometer at 230 nm.
Injection: 20 µl.
Run time: 3.5 times the retention time of lidocaine.
Relative retention with reference to lidocaine (retention time = about 17 min): impurity H = about 0.37; impurity A = about 0.40.
System suitability: reference solution (d):
– *resolution*: minimum 1.5 between the peaks due to impurities H and A.
Limits:
– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.01 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.10 per cent);
– *total*: not more than 5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.5 per cent);
– *disregard limit*: 0.5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 5 ppm.
Dissolve 1.0 g in *water R* and dilute to 25 ml with the same solvent. Carry out the prefiltration. 10 ml of the prefiltrate complies with test E. Prepare the reference solution using 2 ml of *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): 5.5 per cent to 7.0 per cent, determined on 0.25 g.

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

ASSAY

Dissolve 0.220 g in 50 ml of *ethanol (96 per cent) R* and add 5.0 ml of *0.01 M hydrochloric acid*. 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 27.08 mg of $C_{14}H_{23}ClN_2O$.

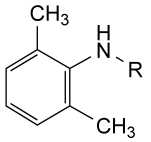
STORAGE

Protected from light.

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, D, E, F, G, H, I, J, K.*



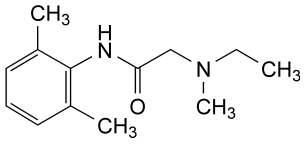
A. R = H: 2,6-dimethylaniline,

C. R = CO-CH_3: *N*-(2,6-dimethylphenyl)acetamide,

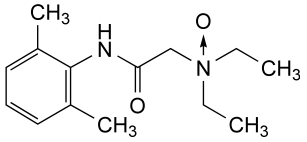
D. R = CO-CH_2-NH-C_2H_5: *N*-(2,6-dimethylphenyl)-2-(ethylamino)acetamide,

G. R = CO-CH_2-NH-$CH(CH_3)_2$: *N*-(2,6-dimethylphenyl)-2-[(1-methylethyl)amino]acetamide,

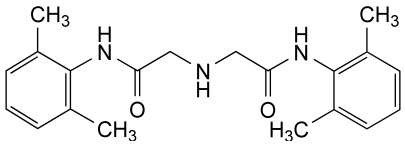
H. R = CO-CH_2-Cl: 2-chloro-*N*-(2,6-dimethylphenyl)acetamide,



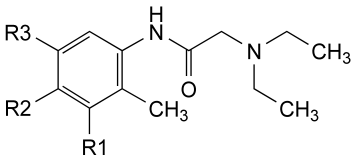
K. R=CO-CH_2-N(CH_3)C_2H_5: *N*-(2,6-dimethylphenyl)-2-(ethylmethylamino)acetamide,



B. 2-(diethylazinoyl)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine N^2-oxide),



E. 2-2′-(azanediyl)bis[*N*-(2,6-dimethylphenyl)acetamide],



F. R1 = CH_3, R2 = R3 = H: 2-(diethylamino)-*N*-(2,3-dimethylphenyl)acetamide,

I. R1 = R3 = H, R2 = CH_3: 2-(diethylamino)-*N*-(2,4-dimethylphenyl)acetamide,

J. R1 = R2 = H, R3 = CH_3: 2-(diethylamino)-*N*-(2,5-dimethylphenyl)acetamide.

01/2008:0957
corrected 6.0

LIME FLOWER

Tiliae flos

DEFINITION

Whole, dried inflorescence of *Tilia cordata* Miller, of *Tilia platyphyllos* Scop., of *Tilia* × *vulgaris* Heyne or a mixture of these.

CHARACTERS

Faint aromatic odour.

Faint, sweet and mucilaginous taste.

IDENTIFICATION

A. The inflorescence is yellowish-green. The main axis of the inflorescence bears a linguiform bract, membranous, yellowish-green, practically glabrous, the central vein of which is joined for up to about half of its length with the peduncle. The inflorescence usually consists of 2-7 flowers, occasionally up to 16. The sepals are detached easily from the perianth; they are up to 6 mm long, their abaxial surface is usually glabrous, their adaxial surface and their borders are strongly pubescent. The 5 spatulate, thin petals are yellowish-white, up to 8 mm long. They show fine venation and their borders only are sometimes covered with isolated trichomes. The numerous stamens are free and usually constitute 5 groups. The superior ovary has a pistil with a somewhat 5-lobate stigma.

B. Separate the inflorescence into its different parts. Examine under a microscope using *chloral hydrate solution R*. The adaxial epidermis of the bract shows cells with straight or slightly sinuous anticlinal walls; the abaxial epidermis shows cells with wavy-sinuous anticlinal walls and anomocytic stomata (*2.8.3*). Isolated cells in the mesophyll contain small calcium oxalate cluster crystals. The parenchyma of the sepals shows, particularly near the veins, numerous mucilaginous cells and cells containing small calcium oxalate clusters. The adaxial epidermis of sepals bears bent, thick-walled covering trichomes, unicellular or stellate with up to 5 cells. The epidermal cells of the petals show straight anticlinal walls with a striated cuticle without stomata. The parenchyma of the petals shows small calcium oxalate clusters and especially in its acuminate part mucilaginous cells. The pollen grains have a diameter of about 30-40 µm and are oval or slightly triangular with 3 germinal pores and a finely granulated exine. The ovary is glabrous or densely covered with trichomes, often very twisted, unicellular or stellate with 2-4 branches.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Shake 1.0 g of the powdered drug (355) (*2.9.12*) with 10 ml of *methanol R* in a water-bath at 65 °C for 5 min. Allow to cool and filter.

Reference solution. Dissolve 2.0 mg of *caffeic acid R*, 5 mg of *hyperoside R* and 5 mg of *rutin R* in 10 ml of *methanol R*.

Plate: *TLC silica gel plate R*.

Mobile phase: *anhydrous formic acid R, water R, methyl ethyl ketone R, ethyl acetate R* (10:10:30:50 *V/V/V/V*).

Application: 10 µl, as bands.

Development: over a path of 15 cm.

Drying: at 100-105 °C.

Detection: spray the warm plate with a 10 g/l solution of *diphenylboric acid aminoethyl ester R* in *methanol R*. Then spray with a 50 g/l solution of *macrogol 400 R* in *methanol R*. Allow to dry for about 30 min and examine in ultraviolet light at 365 nm.

Results: the chromatogram obtained with the reference solution shows in order of increasing R_F value yellowish-orange or brownish-orange fluorescent zones due to rutin and hyperoside and a greenish-blue fluorescent zone due to caffeic acid. In the chromatogram obtained with the test solution, the main zone shows brownish-yellow or orange fluorescence. This zone is situated just above the zone due to hyperoside in the chromatogram obtained with the reference solution. In daylight, this zone stands out from the other zones as the main zone. At the R_F level of rutin there is also