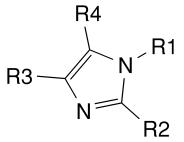
IMPURITIES



A. R1 = R4 = H, R2 = CH_3, R3 = NO_2: 2-methyl-4-nitroimidazole,

B. R1 = R2 = R4 = H, R3 = NO_2: 4-nitroimidazole,

C. R1 = CH_2-CH_2-OH, R2 = R4 = H, R3 = NO_2: 2-(4-nitro-1*H*-imidazol-1-yl)ethanol,

D. R1 = CH_2-CH_2-OH, R2 = R3 = H, R4 = NO_2: 2-(5-nitro-1*H*-imidazol-1-yl)ethanol,

E. R1 = CH_2-CH_2-OH, R2 = CH_3, R3 = NO_2, R4 = H: 2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)ethanol,

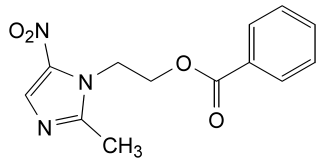
F. R1 = CH_2-CH_2-O-CH_2-CH_2-OH, R2 = CH_3, R3 = H, R4 = NO_2: 2-[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethoxy]ethanol,

G. R1 = CH_2-CO_2H, R2 = CH_3, R3 = H, R4 = NO_2: 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid.

01/2008:0934

METRONIDAZOLE BENZOATE

Metronidazoli benzoas



$C_{13}H_{13}N_3O_4$ M_r 275.3
[13182-89-3]

DEFINITION

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethyl benzoate.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellowish, crystalline powder or flakes.

Solubility: practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in alcohol.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 99 °C to 102 °C.

B. Dissolve 0.100 g in a 103 g/l solution of *hydrochloric acid R* and dilute to 100.0 ml with the same acid. Dilute 1.0 ml of the solution to 100.0 ml with a 103 g/l solution of *hydrochloric acid R*. Examined between 220 nm and 350 nm (*2.2.25*), the solution shows 2 absorption maxima, at 232 nm and 275 nm. The specific absorbance at the absorption maximum at 232 nm is 525 to 575.

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of metronidazole benzoate.*

D. To about 10 mg add about 10 mg of *zinc powder R*, 1 ml of *water R* and 0.3 ml of *hydrochloric acid R*. Heat on a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution. The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution GY_3 (*2.2.2, Method II*).

Dissolve 1.0 g in *dimethylformamide R* and dilute to 10 ml with the same solvent.

Acidity. Dissolve 2.0 g in a mixture of 20 ml of *dimethylformamide R* and 20 ml of *water R*, previously neutralised with *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* using 0.2 ml of *methyl red solution R*. Not more than 0.25 ml of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture. Mix 45 volumes of mobile phase B and 55 volumes of mobile phase A.

Test solution. Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5.0 mg of *metronidazole CRS*, 5.0 mg of *2-methyl-5-nitroimidazole R* and 5.0 mg of *benzoic acid R* in the solvent mixture and dilute to 50.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: spherical *di-isobutyloctadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 180 m^2/g, a pore size of 8 nm and a carbon loading of 10 per cent.

Mobile phase:

– *mobile phase A*: 1.5 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 3.2 with *phosphoric acid R*,

– *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 15	80 → 55	20 → 45
15 - 40	55	45
40 - 41	55 → 80	45 → 20
41 - 45	80	20

Flow rate: 1 ml/min.

Detection: spectrophotometer at 235 nm.

Injection: 10 µl.

Relative retention with reference to metronidazole benzoate (retention time = about 20 min): impurity B = about 0.17; impurity A = about 0.20; impurity C = about 0.7.

System suitability: reference solution (b):

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

Monographs M

Limits:

- *impurities A, B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

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

1.0 g complies with limit test C. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C for 3 h.

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

ASSAY

Dissolve 0.250 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 27.53 mg of $C_{13}H_{13}N_3O_4$.

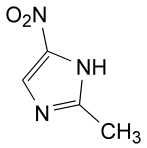
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C.

A. metronidazole,



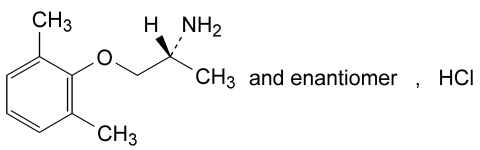
B. 2-methyl-5-nitroimidazole,

C. benzoic acid.

01/2008:1029

MEXILETINE HYDROCHLORIDE

Mexiletini hydrochloridum



$C_{11}H_{18}ClNO$ M_r 215.7
[5370-01-4]

DEFINITION

(2*RS*)-1-(2,6-Dimethylphenoxy)propan-2-amine 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, sparingly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *mexiletine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dilute 1.5 ml of solution S (see Tests) to 15 ml with *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent.

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

Dilute 5 ml of solution S to 10 ml with *water R*.

pH (*2.2.3*): 4.0 to 5.5 for solution S.

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

Test solution. Dissolve 0.500 g of the substance to be examined in *methanol R* and dilute to 5.0 ml with the same solvent.

Reference solution (a). Dissolve the content of a vial of *mexiletine impurity D CRS* in 4.0 ml of *methanol R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 20.0 ml with *methanol R*.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 5.0 ml with *methanol R*.

Reference solution (d). Dilute 1.0 ml of reference solution (a) to 5.0 ml with reference solution (b).

Plate: *TLC silica gel plate R*.

Mobile phase: *concentrated ammonia R, alcohol R, acetone R, toluene R* (3:7:45:45 *V/V/V/V*).

Application: 5 µl of the test solution and reference solutions (c) and (d).

Development: over a path of 10 cm.

Drying: in air.

Detection: spray with *ninhydrin solution R3* and heat at 100-105 °C for 15 min or until the spots appear.

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

Limit:

- *impurity D*: any spot corresponding to impurity D in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.200 g 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 10.0 ml with the mobile phase.