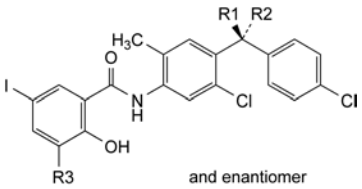


C. R1 = H, R2 = CO_2H, R3 = I: (2*RS*)-[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl)amino]-5-methylphenyl](4-chlorophenyl)acetic acid,

D. R1 = H, R2 = $CONH_2$, R3 = I: *N*-[4-[(1*RS*)-2-amino-1-(4-chlorophenyl)-2-oxoethyl]-5-chloro-2-methylphenyl]-2-hydroxy-3,5-diiodobenzamide,

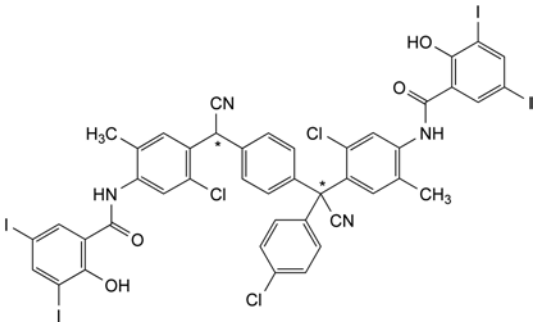
E. R1 = H, R2 = CN, R3 = Cl: 3-chloro-*N*-[5-chloro-4-[(*RS*)-(4-chlorophenyl)cyanomethyl]-2-methylphenyl]-2-hydroxy-5-iodobenzamide,

F. R1 + R2 = O, R3 = I: *N*-[5-chloro-4-(4-chlorobenzoyl)-2-methylphenyl]-2-hydroxy-3,5-diiodobenzamide,

G. R1 = H, R2 = C(=NH)OCH_3, R3 = I: methyl (2*RS*)-2-[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl)amino]-5-methylphenyl]-2-(4-chlorophenyl)acetimidate,

H. R1 = H, R2 = CO-OCH_3, R3 = I: methyl (2*RS*)-[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl)amino]-5-methylphenyl](4-chlorophenyl)acetate,

I. R1 = R3 = H, R2 = CN: *N*-[5-chloro-4-[(*RS*)-(4-chlorophenyl)cyanomethyl]-2-methylphenyl]-2-hydroxy-5-iodobenzamide,

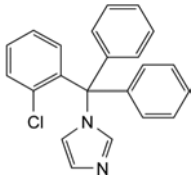


J. *N*-[5-chloro-4-[[4-[[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl)-amino]-5-methylphenyl]cyanomethyl]phenyl](4-chlorophenyl)cyanomethyl]-2-methylphenyl]-2-hydroxy-3,5-diiodobenzamide.

04/2008:0757

CLOTRIMAZOLE

Clotrimazolum



$C_{22}H_{17}ClN_2$ M_r 344.8
[23593-75-1]

DEFINITION

1-[(2-Chlorophenyl)diphenylmethyl]-1*H*-imidazole.

Content: 98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or pale yellow, crystalline powder.

Solubility: practically insoluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 141 °C to 145 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *clotrimazole CRS*.

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

Test solution. Dissolve 50 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution. Dissolve 50 mg of *clotrimazole CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: *concentrated ammonia R1, propanol R, toluene R* (0.5:10:90 *V/V/V*).

Application: 10 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in *acetonitrile R1* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R1*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R1*.

Reference solution (b). Dissolve the contents of a vial of *clotrimazole for peak identification CRS* (containing impurities A, B and F) in 1.0 mL of *acetonitrile R1*.

Reference solution (c). Dissolve 5.0 mg of *imidazole CRS* (impurity D) and 5.0 mg of *clotrimazole impurity E CRS* in *acetonitrile R1* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 25.0 mL with *acetonitrile R1*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* and 0.5 g of *tetrabutylammonium hydrogen sulfate R1* in *water R* and dilute to 1000 mL with the same solvent;
– *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 25	75 → 20	25 → 80
25 - 30	20	80

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL.

Relative retention with reference to clotrimazole (retention time = about 12 min): impurity D = about 0.1; impurity F = about 0.9; impurity B = about 1.1; impurity E = about 1.5; impurity A = about 1.8.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity F and clotrimazole;

– the chromatogram obtained is similar to the chromatogram supplied with *clotrimazole for peak identification CRS*.

Limits:

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

– *impurities D, E*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

– *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

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

– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.300 g in 80 mL of *anhydrous acetic acid R*. Using 0.3 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 34.48 mg of $C_{22}H_{17}ClN_2$.

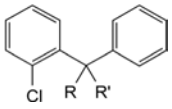
STORAGE

Protected from light.

IMPURITIES

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

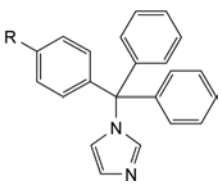
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. R = OH, R′ = C_6H_5: (2-chlorophenyl)diphenylmethanol,

C. R = Cl, R′ = C_6H_5: 1-chloro-2-(chlorodiphenylmethyl)benzene,

E. R + R′ = O: (2-chlorophenyl)phenylmethanone (2-chlorobenzophenone),



B. R = Cl: 1-[(4-chlorophenyl)diphenylmethyl]-1*H*-imidazole,

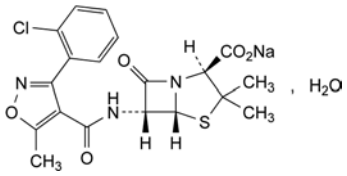
F. R = H: 1-(triphenylmethyl)-1*H*-imidazole (deschloroclotrimazole),

D. imidazole.

01/2008:0661

CLOXACILLIN SODIUM

Cloxacillinum natricum



$C_{19}H_{17}ClN_3NaO_5S,H_2O$ M_r 475.9

[7081-44-9]

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

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

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *cloxacillin sodium CRS*.

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

Test solution. Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a). Dissolve 25 mg of *cloxacillin sodium CRS* in 5 mL of *water R*.

Reference solution (b). Dissolve 25 mg of *cloxacillin sodium CRS*, 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Plate: *TLC silanised silica gel plate R*.

Mobile phase: mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R*, then adjust to pH 5.0 with *glacial acetic acid R*.

Application: 1 µL.

Development: over a path of 15 cm.

Drying: in air.

Detection: expose to iodine vapour until the spots appear; examine in daylight.

System suitability: reference solution (b):

– the chromatogram shows 3 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).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is slightly greenish-yellow. Place the test-tube in a water-bath for 1 min; the solution becomes yellow.