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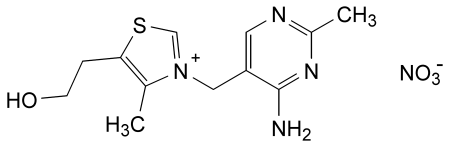
corrected 6.0

THIAMINE NITRATE

Thiamini nitras



$C_{12}H_{17}N_5O_4S$ M_r 327.4
[532-43-4]

DEFINITION

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium nitrate.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or small, colourless crystals.

Solubility: sparingly soluble in water, freely soluble in boiling water, slightly soluble in alcohol and in methanol.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of thiamine nitrate.*

B. Dissolve about 20 mg in 10 ml of *water R*, add 1 ml of *dilute acetic acid R* and 1.6 ml of *1 M sodium hydroxide*, heat on a water-bath for 30 min and allow to cool. Add 5 ml of *dilute sodium hydroxide solution R*, 10 ml of *potassium ferricyanide solution R* and 10 ml of *butanol R* and shake vigorously for 2 min. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm. Repeat the test using 0.9 ml of *1 M sodium hydroxide* and 0.2 g of *sodium sulphite R* instead of 1.6 ml of *1 M sodium hydroxide*. Practically no fluorescence is produced.

C. About 5 mg gives the reaction of nitrates (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 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_7 (*2.2.2, Method II*).

pH (*2.2.3*): 6.8 to 7.6 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Solution A. Add 5 volumes of *glacial acetic acid R* to 95 volumes of *water R* and mix.

Test solution. Dissolve 0.35 g of the substance to be examined in 15.0 ml of solution A and dilute to 100.0 ml with *water R*.

Reference solution (a). Dissolve 5 mg of the substance to be examined and 5 mg of *thiamine impurity E CRS* in 4 ml of solution A and dilute to 25.0 ml with *water R*. Dilute 5.0 ml of the solution to 25.0 ml with *water R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with *water R*.

Column:
- *size*: *l* = 0.25 m, Ø = 4.0 mm,
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm,
- *temperature*: 45 °C.

Mobile phase:
- *mobile phase A*: 3.764 g/l solution of *sodium hexanesulphonate R* adjusted to pH 3.1 with *phosphoric acid R*,
- *mobile phase B*: *methanol R2*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	90 → 70	10 → 30
25 - 33	70 → 50	30 → 50
33 - 40	50	50
40 - 45	50 → 90	50 → 10

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 248 nm.

Injection: 25 µl.

Relative retention with reference to thiamine (retention time = about 30 min): impurity A = about 0.3; impurity B = about 0.9; impurity C = about 1.2.

System suitability: reference solution (a):
- *resolution*: minimum 1.6 between the peaks due to impurity E and to thiamine.

Limits:
- *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),
- *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent),
- *disregard limit*: 0.05 times 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.

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

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.140 g in 5 ml of *anhydrous formic acid R* and add 50 ml of *acetic anhydride R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and carrying out the titration within 2 min. Carry out a blank titration.

1.0 ml of *0.1 M perchloric acid* is equivalent to 16.37 mg of $C_{12}H_{17}N_5O_4S$.

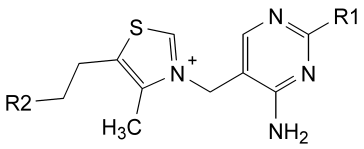
STORAGE

In a non-metallic container, protected from light.

IMPURITIES

Specified impurities: A, B, C.

Other detectable impurities: D, E, F, G, H.



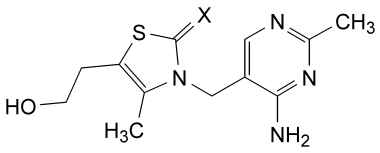
A. R1 = CH_3, R2 = O-SO_3^-: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-5-[2-(sulphonatooxy)ethyl]thiazolium (thiamine sulphate ester),

B. R1 = H, R2 = OH: 3-[(4-aminopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium (desmethylthiamine),

C. R1 = CH_3, R2 = Cl: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-chloroethyl)-4-methylthiazolium (chlorothiamine),

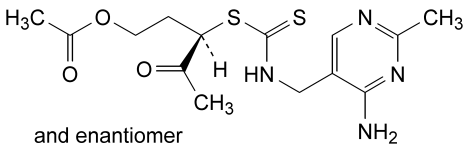
F. R1 = C_2H_5, R2 = OH: 3-[(4-amino-2-ethylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium (ethylthiamine),

G. R1 = CH_3, R2 = O-CO-CH_3: 5-[2-(acetyloxy)ethyl]-3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methylthiazolium (acetylthiamine),



D. X = O: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazol-2(3*H*)-one (oxothiamine),

E. X = S: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazol-2(3*H*)-thione (thioxothiamine),



H. (3*RS*)-3-[[[(4-amino-2-methylpyrimidin-5-yl)methyl]thiocarbamoyl]sulphanyl]-4-oxopentyl acetate (ketodithiocarbamate).

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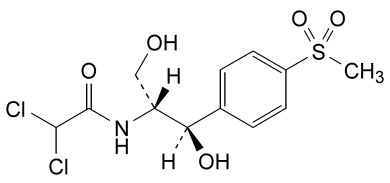
THIAMPHENICOL

Thiamphenicolum



$C_{12}H_{15}Cl_2NO_5S$ M_r 356.2
[15318-45-3]

DEFINITION

2,2-Dichloro-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)-2-[4-(methylsulphonyl)phenyl]ethyl]acetamide.

Content: 98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: fine, white or yellowish-white, crystalline powder or crystals.

Solubility: slightly soluble in water, very soluble in dimethylacetamide, freely soluble in acetonitrile and in dimethylformamide, soluble in methanol, sparingly soluble in acetone and in anhydrous ethanol, slightly soluble in ethyl acetate.

A solution in anhydrous ethanol is dextrorotatory and a solution in dimethylformamide is laevorotatory.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dry the substance to be examined and the reference substance at 100-105 °C for 2 h; examine as discs of *potassium bromide R*.

Comparison: *thiamphenicol CRS*.

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

Test solution. Dissolve 0.1 g of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 0.1 g of *thiamphenicol CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Plate: *silica gel* GF_{254} *R* as the coating substance.

Mobile phase: *methanol R, ethyl acetate R* (3:97 *V/V*).

Application: 5 µl.

Development: over a path of 10 cm.

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 spot in the chromatogram obtained with the reference solution.

C. To 50 mg in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 ml of *dilute nitric acid R* and filter. To 1 ml of the filtrate add 1 ml of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Acidity or alkalinity. Shake 0.1 g with 20 ml of *carbon dioxide-free water R* and add 0.1 ml of *bromothymol blue solution R1*. Not more than 0.1 ml of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*): – 21 to – 24 (dried substance).

Dissolve 1.25 g in *dimethylformamide R* and dilute to 25.0 ml with the same solvent.

Melting point (*2.2.14*): 163 °C to 167 °C.

Absorbance (*2.2.25*).

Test solution (a). Dissolve 20 mg in *water R*, heating to about 40 °C, and dilute to 100.0 ml with the same solvent.

Test solution (b). Dilute 2.5 ml of test solution (a) to 50.0 ml with *water R*.

Spectral range: 240-300 nm for test solution (a); 200-240 nm for test solution (b).

Absorption maxima: at 266 nm and 273 nm for test solution (a); at 224 nm for test solution (b).

ERRATA

In the following monographs, after the heading ‘Other detectable impurities’ in the Impurities section, read:

‘(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*)’

Articaine hydrochloride (1688)
Biperiden hydrochloride (1074)
Caffeine (0267)
Caffeine monohydrate (0268)
Ibuprofen (0721)
Ifosfamide (1529)
Metformin hydrochloride (0931)
Naphazoline hydrochloride (0730)
Norethisterone acetate (0850)
Oxaliplatin (2017)
Potassium clavulanate (1140)
Potassium clavulanate, diluted (1653)
Testosterone propionate (0297)
Thiamine hydrochloride (0303)
Thiamine nitrate (0531)
Tranexamic acid (0875)