Test solution. Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 20.0 ml with the solvent mixture.

Reference solution (a). Dissolve 10 mg of *piretanide CRS* and 3 mg of *piretanide impurity A CRS* in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution (b). Dilute 0.3 ml of the test solution to 100.0 ml with the solvent mixture.

Column:

– *size*: *l* = 0.125 m, Ø = 4 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: a mixture of 35 volumes of *acetonitrile R1* and 65 volumes of a solution prepared as follows: add 1 ml of *trifluoroacetic acid R* to 500 ml of *water for chromatography R*, add 1 ml of *triethylamine R* and dilute to 1000 ml with *water for chromatography R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 232 nm.

Injection: 10 µl.

Run time: 5 times the retention time of piretanide.

Relative retention with reference to piretanide (retention time = about 10 min): impurity A = about 0.9.

System suitability: reference solution (a):

– *resolution*: minimum 2 between the peaks due to impurity A and piretanide.

Limits:

– *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

– *total*: not more than 3.33 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution 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 105 °C for 4 h.

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

ASSAY

Dissolve 0.300 g in 25 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

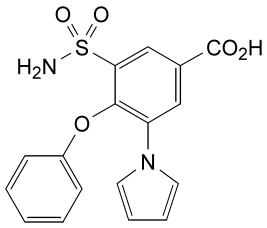
1 ml of *0.1 M perchloric acid* is equivalent to 36.24 mg of $C_{17}H_{18}N_2O_5S$.

STORAGE

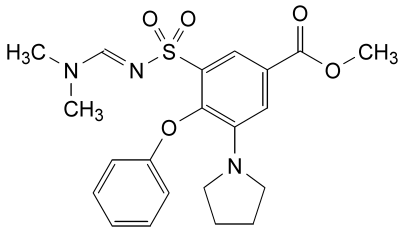
Protected from light.

IMPURITIES

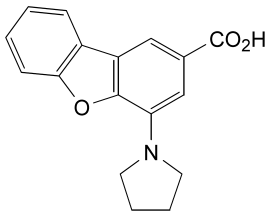
Specified impurities: A, B, C.



A. 4-phenoxy-3-(1*H*-pyrrol-1-yl)-5-sulphamoylbenzoic acid,



B. methyl-3-[[(dimethylamino)methylene]sulphamoyl]-4-phenoxy-5-(pyrrolidin-1-yl)benzoate,

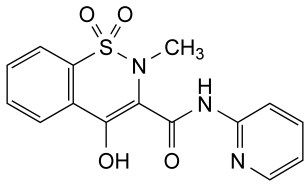


C. 4-(pyrrolidin-1-yl)dibenzo[*b*,*d*]furan-2-carboxylic acid.

01/2008:0944
corrected 6.0

PIROXICAM

Piroxicamum



$C_{15}H_{13}N_3O_4S$ M_r 331.4
[36322-90-4]

DEFINITION

4-Hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

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

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

Solubility: practically insoluble in water, soluble in methylene chloride, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of *potassium bromide R*.

Comparison: *piroxicam CRS*.

Monographs P

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 75 mg of the substance to be examined in *acetonitrile R*, warming slightly if necessary, and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dissolve 5 mg of *piroxicam for system suitability CRS* in *acetonitrile R* and dilute to 25.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of the test solution to 10.0 ml with *acetonitrile R*. Dilute 1.0 ml of this solution to 50.0 ml with *acetonitrile R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase: mix 40 volumes of *acetonitrile R* and 60 volumes of a 6.81 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µl.

Run time: 5 times the retention time of piroxicam.

System suitability: reference solution (a):

– *relative retention* with reference to piroxicam: impurity B = about 0.85;

– *symmetry factor*: maximum 1.5 for the peak due to impurity B;

– the chromatogram obtained is similar to the chromatogram supplied with *piroxicam for system suitability CRS*.

Limits:

– *impurities A, B, C, D, E, F, G, H, I, J, K, L*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

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

1.0 g complies with test C. Prepare the reference solution 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 vacuo* at 105 °C for 4 h.

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

ASSAY

Dissolve 0.250 g in 60 ml of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

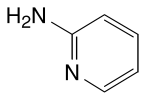
1 ml of *0.1 M perchloric acid* is equivalent to 33.14 mg of $C_{15}H_{13}N_3O_4S$.

STORAGE

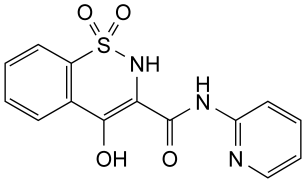
In an airtight container, protected from light.

IMPURITIES

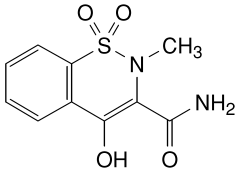
Specified impurities: *A, B, C, D, E, F, G, H, I, J, K, L.*



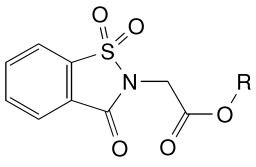
A. pyridin-2-amine,



B. 4-hydroxy-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



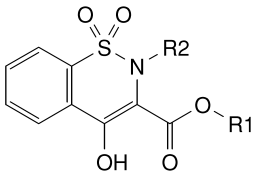
C. 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



D. R = CH_3: methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,

E. R = C_2H_5: ethyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,

F. R = $CH(CH_3)_2$: 1-methylethyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,



G. R1 = CH_3, R2 = H: methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,

H. R1 = C_2H_5, R2 = H: ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,

I. R1 = $CH(CH_3)_2$, R2 = H: 1-methylethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,

J. R1 = R2 = CH_3: methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,

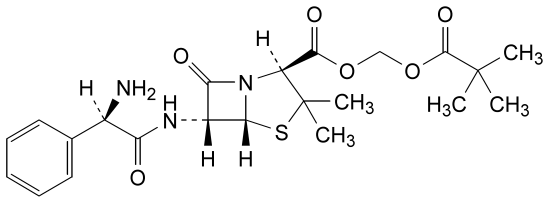
K. R1 = C_2H_5, R2 = CH_3: ethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,

L. R1 = $CH(CH_3)_2$, R2 = CH_3: 1-methylethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide.

01/2008:0852
corrected 6.0

PIVAMPICILLIN

Pivampicillinum



$C_{22}H_{29}N_3O_6S$ M_r 463.6
[33817-20-8]

DEFINITION

Methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate 2,2-dimethylpropanoate.

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, crystalline powder.

Solubility: practically insoluble in water, freely soluble in methanol, soluble in anhydrous ethanol. It dissolves in dilute acids.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *pivampicillin CRS*.

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

Test solution. Dissolve 10 mg of the substance to be examined in 2 ml of *methanol R*.

Reference solution (a). Dissolve 10 mg of *pivampicillin CRS* in 2 ml of *methanol R*.

Reference solution (b). Dissolve 10 mg of *bacampicillin hydrochloride CRS*, 10 mg of *pivampicillin CRS* and 10 mg of *talampicillin hydrochloride CRS* in 2 ml of *methanol R*.

Plate: *TLC silanised silica gel plate R*.

Mobile phase: mix 10 volumes of a 272 g/l solution of *sodium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*, 40 volumes of *water R* and 50 volumes of *ethanol (96 per cent) R*.

Application: 1 µl.

Development: over a path of 15 cm.

Drying: in a current of warm air.

Detection: spray with *ninhydrin solution R1* and heat at 60 °C for 10 min.

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 *sulphuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is almost colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

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 B_7 (*2.2.2, Method I*).

Dissolve 50 mg in 12 ml of *0.1 M hydrochloric acid*.

Specific optical rotation (*2.2.7*): + 208 to + 222 (anhydrous substance).

Dissolve 0.100 g in 5.0 ml of *ethanol (96 per cent) R* and dilute to 10.0 ml with *0.1 M hydrochloric acid*.

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

Test solution. Dissolve 0.100 g of the substance to be examined in 1.0 ml of a mixture of 1 volume of *water R* and 9 volumes of *acetonitrile R*.

Reference solution. Dissolve 5.0 mg of *triethanolamine R* in a mixture of 1 volume of *water R* and 9 volumes of *acetonitrile R* and dilute to 100 ml with the same mixture of solvents.

Plate: *TLC silica gel plate R*.

Mobile phase: *methanol R, butanol R, phosphate buffer solution pH 5.8 R, glacial acetic acid R, butyl acetate R* (5:15:24:40:80 *V/V/V/V/V*).

Application: 10 µl.

Development: over a path of 12 cm.

Drying: at 110 °C for 10 min and allow to cool.

Chlorine treatment: place at the bottom of a chromatographic tank an evaporating dish containing a mixture of 1 volume of *hydrochloric acid R1*, 1 volume of *water R* and 2 volumes of a 15 g/l solution of *potassium permanganate R*; close the tank and allow to stand for 15 min; place the dried plate in the tank and close the tank; leave the plate in contact with the chlorine vapour in the tank for 15-20 min; withdraw the plate and allow it to stand in air for 2-3 min.

Detection: spray with *tetramethyldiaminodiphenylmethane reagent R*.