– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent),
– *any other impurity*: not more than the area of the peak due to nifedipine in the chromatogram obtained with reference solution (c) (0.1 per cent),
– *total*: not more than 0.3 per cent,
– *disregard limit*: 0.1 times the area of the peak due to nifedipine in the chromatogram obtained with reference solution (c) (0.01 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 for 2 h.

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

ASSAY

Dissolve 0.1300 g in a mixture of 25 ml of *2-methyl-2-propanol R* and 25 ml of *perchloric acid solution R*. Titrate with *0.1 M cerium sulphate* using 0.1 ml of *ferroin R* as indicator, until the pink colour disappears. Titrate slowly towards the end of the titration. Carry out a blank titration.

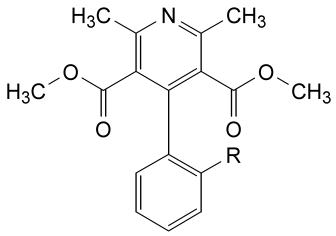
1 ml of *0.1 M cerium sulphate* is equivalent to 17.32 mg of $C_{17}H_{18}N_2O_6$.

STORAGE

Protected from light.

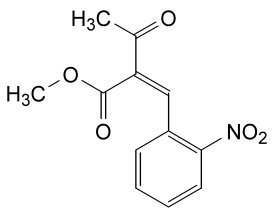
IMPURITIES

Specified impurities: A, B, C, D.

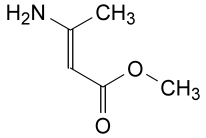


A. R = NO_2: dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (nitrophenylpyridine analogue),

B. R = NO: dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (nitrosophenylpyridine analogue),



C. methyl 2-(2-nitrobenzylidene)-3-oxobutanoate,

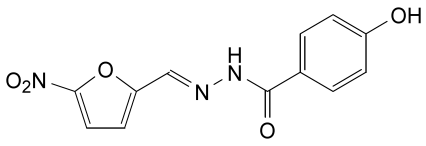


D. methyl 3-aminobut-2-enoate.

01/2008:1999
corrected 6.0

NIFUROXAZIDE

Nifuroxazidum



$C_{12}H_9N_3O_5$ M_r 275.2
[965-52-6]

DEFINITION

1-(4-Hydroxybenzoyl)-2-[(5-nitrofuran-2-yl)methylene]-diazane.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: bright yellow, crystalline powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of nifuroxazide.*

TESTS

Specific absorbance (*2.2.25*): 940 to 1000 at the absorption maximum at 367 nm.

Protected from light, dissolve 10.0 mg in 10 ml of *ethylene glycol monomethyl ether R* and dilute to 100.0 ml with *methanol R*. Dilute 5.0 ml of this solution to 100.0 ml with *methanol R*.

Impurity A: maximum 0.05 per cent.

Test solution (a). Dissolve 1.0 g of the substance to be examined in *dimethyl sulphoxide R* and dilute to 10.0 ml with the same solvent.

Test solution (b). To 5.5 ml of test solution (a) add 50.0 ml of *water R* while stirring. Allow to stand for 15 min and filter.

Reference solution. To 0.5 ml of test solution (a) add 5.0 ml of a 50 mg/l solution of *4-hydroxybenzohydrazide R* in *dimethyl sulphoxide R*. Add 50.0 ml of *water R* while stirring. Allow to stand for 15 min and filter.

Add 0.5 ml of *phosphomolybdotungstic reagent R* and 10.0 ml of *sodium carbonate solution R* separately to 10.0 ml of test solution (b) and to 10.0 ml of the reference solution. Allow to stand for 1 h. Examine the 2 solutions at 750 nm. The absorbance (*2.2.25*) of the solution obtained with test solution (b) is not greater than that obtained with the reference solution.

Related substances. Liquid chromatography (*2.2.29*). *Use freshly prepared solutions, protected from light.*

Test solution. Dissolve 0.100 g of the substance to be examined in 15.0 ml of *dimethylformamide R* and dilute to 100.0 ml with the mobile phase. If precipitation occurs, use the supernatant liquid.

Reference solution (a). Dissolve 10.0 mg of *methyl parahydroxybenzoate R* (impurity B) in 2.0 ml of *dimethylformamide R* and dilute to 20.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 10 mg of *methyl parahydroxybenzoate R* in 2 ml of *dimethylformamide R* and dilute to 20 ml with the mobile phase. Dilute 1 ml of this solution to 100 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 340 m^2/g, a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase: *acetonitrile R, water R* (35:65 *V/V*).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µl.

Run time: 6 times the retention time of nifuroxazide.

Relative retention with reference to nifuroxazide (retention time = about 6.5 min): impurity A = about 0.4; impurity B = about 1.2; impurity C = about 2.8; impurity D = about 5.2.

System suitability: reference solution (b):

– *resolution*: minimum 3.0 between the peaks due to nifuroxazide and impurity B.

Limits:

– *any impurity*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and not more than 1 such peak has an area greater than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (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 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

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

ASSAY

Dissolve 0.200 g, if necessary with heating, in 30 ml of *dimethylformamide R* and add 20 ml of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

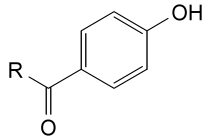
1 ml of *0.1 M sodium hydroxide* is equivalent to 27.52 mg of $C_{12}H_9N_3O_5$.

STORAGE

Protected from light.

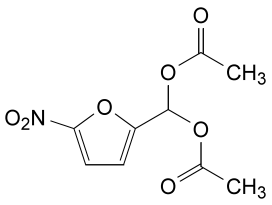
IMPURITIES

Specified impurities: A, B, C, D.

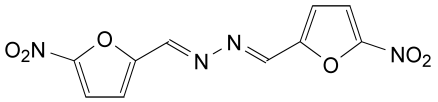


A. R = $NH\text{-}NH_2$: (4-hydroxybenzoyl)diazane (*p*-hydroxybenzohydrazide),

B. R = OCH_3: methyl 4-hydroxybenzoate,



C. (5-nitrofuran-2-yl)methylene diacetate,

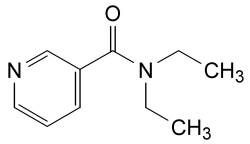


D. 1,2-bis[(5-nitrofuran-2-yl)methylene]diazane (5-nitrofurfural azine).

01/2008:0233

NIKETHAMIDE

Nicethamidum



$C_{10}H_{14}N_2O$ M_r 178.2
[59-26-7]

DEFINITION

Nikethamide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of *N,N*-diethylpyridine-3-carboxamide, calculated with reference to the anhydrous substance.

CHARACTERS

An oily liquid or a crystalline mass, colourless or slightly yellowish, miscible with water and with alcohol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Dissolve 0.15 g in *0.01 M hydrochloric acid* and dilute to 100.0 ml with the same acid. Dilute 1.0 ml of this solution to 100.0 ml with *0.01 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*) in a 2 cm cell, the solution shows a single absorption maximum, at 263 nm. The specific absorbance at the maximum is about 285.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *nikethamide CRS*.

C. Heat 0.1 g with 1 ml of *dilute sodium hydroxide solution R*. Diethylamine is evolved progressively and is recognisable by its characteristic odour and by its turning *red litmus paper R* blue.

D. Dilute 1 ml of solution S (see Tests) to 250 ml with *water R*. To 2 ml of this solution add 2 ml of *cyanogen bromide solution R*. Add 3 ml of a 25 g/l solution of *aniline R* and shake. A yellow colour develops.

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent.