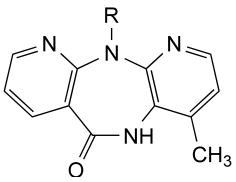


A. R = C_2H_5: 11-ethyl-4-methyl-5,11-dihydro-6*H*-dipyrido [3,2-b:2′,3′-*e*][1,4]diazepin-6-one,

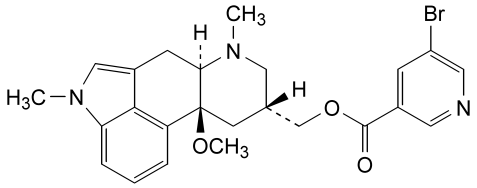
B. R = H: 4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-b:2′,3′-*e*][1, 4]diazepin-6-one,

C. R = CH_2-CH_2-CH3: 4-methyl-11-propyl-5,11-dihydro-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one.

01/2008:1998

NICERGOLINE

Nicergolinum



$C_{24}H_{26}BrN_3O_3$ M_r 484.4
[27848-84-6]

DEFINITION

[(6a*R*,9*R*,10a*S*)-10a-Methoxy-4,7-dimethyl-4,6,6a,7,8, 9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: fine to granular, white or yellowish powder.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Specific optical rotation (*2.2.7*): + 4.8 to + 5.8 (anhydrous substance).

Dissolve 0.50 g in *alcohol R* and dilute to 10.0 ml with the same solvent.

B. Dissolve 50.0 mg in *alcohol R* and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml to 50.0 ml with *alcohol R*. Examined between 220 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 288 nm and an absorption minimum at 251 nm. The specific absorbance at the maximum at 288 nm is 175 to 185 (anhydrous substance).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

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

If the spectra obtained show differences, dissolve the substance to be examined in *alcohol R*, evaporate to dryness and record a further spectrum using the residue.

D. Dissolve 2 mg in 2 ml of *sulphuric acid R*. A blue 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 intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 0.5 g in *alcohol R* and dilute to 10 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg in *acetonitrile R* and dilute to 25.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile R*. Dilute 10.0 ml of this solution to 50.0 ml with *acetonitrile R*.

Reference solution (b). Dissolve 25.0 mg of the substance to be examined and 10.0 mg of *nicergoline impurity A CRS* in *acetonitrile R* and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml to 100.0 ml with *acetonitrile R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

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

Mobile phase: mix 30 volumes of *acetonitrile R*, 35 volumes of *methanol R* and 35 volumes of a freshly prepared solution of 6.8 g/l *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with *triethylamine R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 288 nm.

Injection: 20 µl.

Run time: twice the retention time of nicergoline.

Relative retention with reference to nicergoline (retention time = about 25 min): impurity B = 0.5.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to nicergoline and impurity A.

Limits:

– *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent),

– *any other impurity*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and not more than 2 such peaks have an area greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *total*: not more than 7.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent),

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.32*): maximum 0.5 per cent, determined on 0.100 g.

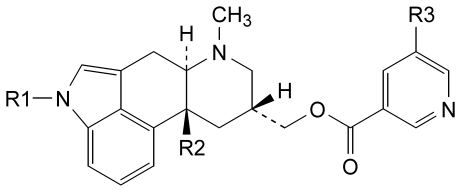
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 ml of *acetone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Titrate to the 1st point of inflexion.

1 ml of *0.1 M perchloric acid* is equivalent to 48.44 mg of $C_{24}H_{26}BrN_3O_3$.

IMPURITIES

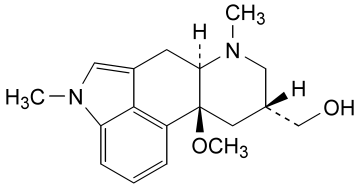


A. R1 = CH_3, R2 = OCH_3, R3 = Cl: [(6a*R*,9*R*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-chloropyridine-3-carboxylate,

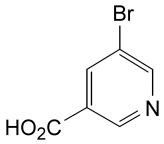
B. R1 = H, R2 = OCH_3, R3 = Br: [(6a*R*,9*R*,10a*S*)-10a-methoxy-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate,

E. R1 = CH_3, R2 = OH, R3 = Br: [(6a*R*,9*R*,10a*S*)-10a-hydroxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate,

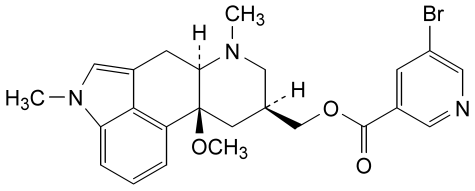
G. R1 = CH_3, R2 = H, R3 = Br: [(6a*R*,9*R*,10a*R*)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate



C. [(6a*R*,9*R*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methanol,



D. 5-bromopyridine-3-carboxylic acid,

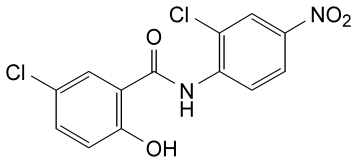


F. [(6a*R*,9*S*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate.

01/2008:0679
corrected 6.0

NICLOSAMIDE, ANHYDROUS

Niclosamidum anhydricum



$C_{13}H_8Cl_2N_2O_4$ M_r 327.1
[50-65-7]

DEFINITION

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.

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

CHARACTERS

Appearance: yellowish-white or yellowish, fine crystals.

Solubility: practically insoluble in water, sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 227 °C to 232 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs prepared using about 0.5 mg of substance and 0.3 g of *potassium bromide R*.

Comparison: *anhydrous niclosamide CRS*.

C. To 50 mg add 5 ml of *1 M hydrochloric acid* and 0.1 g of *zinc powder R*, heat in a water-bath for 10 min, cool and filter. To the filtrate add 1 ml of a 5 g/l solution of *sodium nitrite R* and allow to stand for 3 min; add 2 ml of a 20 g/l solution of *ammonium sulphamate R*, shake, allow to stand for 3 min and add 2 ml of a 5 g/l solution of *naphthylethylenediamine dihydrochloride R*. A violet colour is produced.

D. Heat the substance on a copper wire in a non-luminous flame. The flame becomes green.

E. Loss on drying (see Tests).

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R*, heating gently, cool and dilute to 50.0 ml with the same solvent.

Reference solution. Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile R*. Dilute 1.0 ml of this solution to 20.0 ml with *acetonitrile R*.

Column:

– *size*: *l* = 0.125 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mixture of equal volumes of *acetonitrile R* and a solution containing 2 g/l of *potassium dihydrogen phosphate R*, 1 g/l of *disodium hydrogen phosphate R* and 2 g/l of *tetrabutylammonium hydrogen sulphate R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µl.