**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.

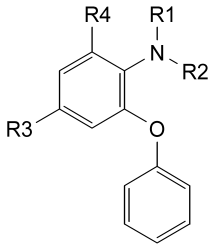
**Sulphated ash** (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.240 g in 30 ml of previously neutralised *acetone 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 30.83 mg of $C_{13}H_{12}N_2O_5S$.

IMPURITIES




A. R1 = $SO_2$-$CH_3$, R2 = H, R3 = R4 = $NO_2$: *N*-(2,4-dinitro-6-phenoxyphenyl)methanesulphonamide,

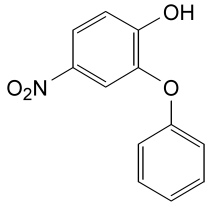
B. R1 = $SO_2$-$CH_3$, R2 = R3 = R4 = H: *N*-(2-phenoxyphenyl)methanesulphonamide,

C. R1 = R2 = R3 = R4 = H: 2-phenoxyaniline,

D. R1 = R2 = R4 = H, R3 = $NO_2$: 4-nitro-2-phenoxyaniline,

E. R1 = R2 = $SO_2$-$CH_3$, R3 = R4 = H: *N*,*N*-bis(methylsulphonyl)-2-phenoxyaniline,

F. R1 = R2 = $SO_2$-$CH_3$, R3 = $NO_2$, R4 = H: *N*,*N*-bis(methylsulphonyl)-4-nitro-2-phenoxyaniline,

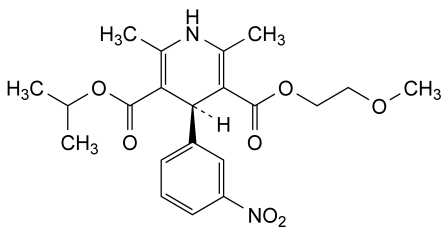



G. 4-nitro-2-phenoxyphenol.

**01/2008:1245**
**corrected 6.0**

# NIMODIPINE

## Nimodipinum




and enantiomer

$C_{21}H_{26}N_2O_7$ $M_r$ 418.4
[66085-59-4]

DEFINITION

2-Methoxyethyl 1-methylethyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

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

CHARACTERS

*Appearance*: light yellow or yellow, crystalline powder.

*Solubility*: practically insoluble in water, freely soluble in ethyl acetate, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

*Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).*

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *nimodipine CRS*.

If the spectra obtained in the solid state show differences, record new spectra using 20 g/l solutions in *methylene chloride R* and a 0.2 mm cell.

TESTS

**Solution S**. Dissolve 1.0 g in *acetone R* and dilute to 20.0 ml with the same solvent.

**Appearance of solution**. Solution S is clear (*2.2.1*).

**Optical rotation** (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution.* Dissolve 40.0 mg of the substance to be examined in 2.5 ml of *tetrahydrofuran R* and dilute to 25.0 ml with the mobile phase.

*Reference solution (a).* Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 10.0 ml with the mobile phase.

*Reference solution (b). Nimodipine impurity A CRS.*

*Reference solution (c).* Dilute the test solution as described in the leaflet accompanying *nimodipine impurity A CRS.*

*Reference solution (d).* Mix reference solution (b) and reference solution (c) as described in the leaflet accompanying *nimodipine impurity A CRS.*

*Column*:

– *size*: *l* = 0.125 m, Ø = 4.6 mm;

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

– *temperature*: 40 °C.

*Mobile phase*: *methanol R, tetrahydrofuran R, water R* (20:20:60 *V/V/V*).

*Flow rate*: 2.0 ml/min.

*Detection*: spectrophotometer at 235 nm.

*Injection*: 20 µl of the test solution and reference solutions (a) and (d).

*Run time*: 4 times the retention time of nimodipine.

*Retention time*: impurity A = about 7 min; nimodipine = about 8 min.

*System suitability*: reference solution (d):

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

*Limits*:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

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

– *total*: not more than 2.5 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 peak due to nimodipine in the chromatogram obtained with reference solution (d) (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.

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

ASSAY

Dissolve with gentle heating 0.180 g in a mixture of 25 ml of *2-methyl-2-propanol R* and 25 ml of *perchloric acid solution R*. Add 0.1 ml of *ferroin R*. Titrate with *0.1 M cerium sulphate*. Titrate slowly towards the end of the titration. Carry out a blank titration.

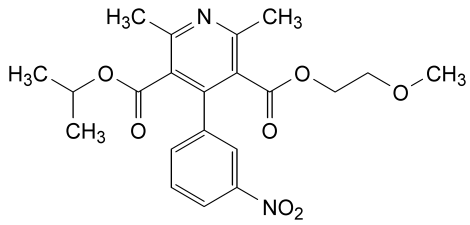
1 ml of *0.1 M cerium sulphate* is equivalent to 20.92 mg of $C_{21}H_{26}N_2O_7$.

STORAGE

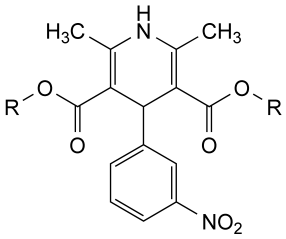
Protected from light.

IMPURITIES

*Specified impurities: A, B, C.*



A. 2-methoxyethyl 1-methylethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate,



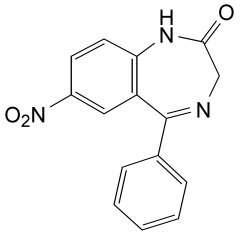
B. R = $CH(CH_3)_2$: bis(1-methylethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,

C. R = $CH_2$-$CH_2$-$OCH_3$: bis(2-methoxyethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

**01/2008:0415**
**corrected 6.0**

# NITRAZEPAM

## Nitrazepamum



$C_{15}H_{11}N_3O_3$ $M_r$ 281.3
[146-22-5]

DEFINITION

Nitrazepam contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 7-nitro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, calculated with reference to the dried substance.

CHARACTERS

A yellow, crystalline powder, practically insoluble in water, slightly soluble in alcohol.

IDENTIFICATION

*First identification: A, C.*

*Second identification: A, B, D, E.*

A. Melting point (*2.2.14*): 226 °C to 230 °C.

B. *Protect the solutions from light and measure the absorbances immediately.* Dissolve 25.0 mg in a 5 g/l solution of *sulphuric acid R* in *methanol R* and dilute to 250.0 ml with the same solvent. Dilute 5.0 ml of the solution to 100.0 ml with a 5 g/l solution of *sulphuric acid R* in *methanol R*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 280 nm. The specific absorbance at the maximum is 890 to 950.

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

D. Dissolve about 20 mg in a mixture of 5 ml of *hydrochloric acid R* and 10 ml of *water R*. Boil for 5 min, cool and add 2 ml of a 1 g/l solution of *sodium nitrite R*. Allow to stand for 1 min and add 1 ml of a 5 g/l solution of *sulphamic acid R* and mix. Allow to stand for 1 min and add 1 ml of a 1 g/l solution of *naphthylethylenediamine dihydrochloride R*. A red colour is produced.

E. Dissolve about 10 mg in 1 ml of *methanol R*, warming if necessary, and add 0.05 ml of *dilute sodium hydroxide solution R*. An intense yellow colour is produced.

TESTS

**Related substances**. *Carry out the test protected from light.* Examine by thin-layer chromatography (*2.2.27*), using *silica gel* $GF_{254}$ *R* as the coating substance.

*Test solution.* Dissolve 0.2 g of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent. Prepare the solution immediately before use.