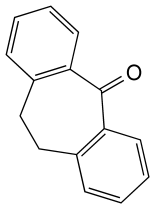
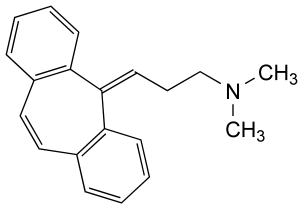
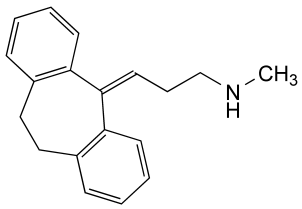


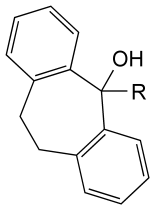
A. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (dibenzosuberone),



B. 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine (cyclobenzaprine),

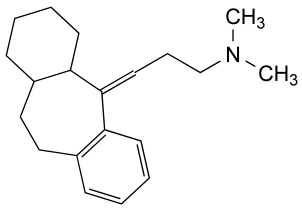


C. 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (nortriptyline),

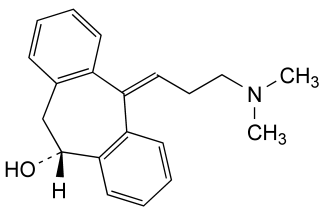


D. R = CH_2-CH_2-CH_2-N(CH_3)$_2$: 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol,

G. R = H: 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (dibenzosuberol),



E. *N*,*N*-dimethyl-3-(1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propan-1-amine,

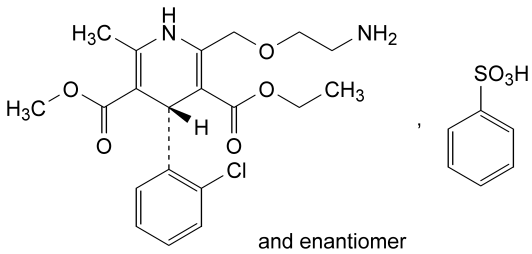


F. (5*EZ*,10*RS*)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-10-ol.

01/2008:1491

AMLODIPINE BESILATE

Amlodipini besilas



$C_{26}H_{31}ClN_2O_8S$ M_r 567.1
[111470-99-6]

DEFINITION

3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *amlodipine besilate CRS.*

Preparation: mulls.

B. Examine the chromatograms obtained in test A for related substances in ultraviolet light at 366 nm.

Results: the principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

C. Dissolve 5.0 mg in a 1 per cent *V/V* solution of *0.1 M hydrochloric acid* in *methanol R* and dilute to 100.0 ml with the same acid solution. Examined between 300 nm and 400 nm (*2.2.25*), the solution shows an absorption maximum at 360 nm. The specific absorbance at the maximum is 113 to 121.

TESTS

Optical rotation (*2.2.7*): – 0.10° to + 0.10°.

Dissolve 0.250 g in *methanol R* and dilute to 25.0 ml with the same solvent.

Related substances

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

Test solution (a). Dissolve 0.140 g of the substance to be examined in *methanol R* and dilute to 2.0 ml with the same solvent.

Test solution (b). Dilute 1.0 ml of test solution (a) to 10.0 ml with *methanol R.*

Reference solution (a). Dissolve 70.0 mg of *amlodipine besilate CRS* in 1.0 ml of *methanol R.*

Reference solution (b). Dilute 1 ml of reference solution (a) to 10 ml with *methanol R.*

Reference solution (c). Dilute 3.0 ml of test solution (b) to 100.0 ml with *methanol R*.

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

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: the upper layer of a mixture of *glacial acetic acid R*, *water R* and *methyl isobutyl ketone R* (25:25:50 *V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: for 15 min at 80 °C.

Detection: examine in ultraviolet light at 254 nm and 366 nm.

System suitability: the chromatogram obtained with reference solution (a) shows 2 clearly separated minor spots with R_F values of about 0.18 and 0.22.

Limits: in the chromatogram obtained with test solution (a):

– *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.3 per cent) and at most 2 spots are more intense than the spot in the chromatogram obtained with reference solution (d) (0.1 per cent).

B. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Test solution (b). Dilute 5.0 ml of test solution (a) to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *amlodipine besilate CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). Dilute 3.0 ml of test solution (a) to 100.0 ml with the mobile phase and dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution (c). Dissolve 5 mg of the substance to be examined in 5 ml of *strong hydrogen peroxide solution R*. Heat at 70 °C for 45 min.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm,

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

Mobile phase: mix 15 volumes of *acetonitrile R*, 35 volumes of *methanol R* and 50 volumes of a solution prepared as follows: dissolve 7.0 ml of *triethylamine R* in 1 litre of *water R* and adjust to pH 3.0 ± 0.1 with *phosphoric acid R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 237 nm.

Injection: 10 µl; inject test solution (a) and reference solutions (b) and (c).

Run time: 3 times the retention time of amlodipine.

Relative retention with reference to amlodipine (retention time = about 7 min): impurity D = about 0.5.

System suitability: reference solution (c):

– *resolution*: minimum 4.5 between the peaks corresponding to amlodipine and impurity D.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity D by 2,

– *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *total of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent); disregard any peak due to benzene sulphonate (relative retention = about 0.2),

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

Water (*2.5.12*): maximum 0.5 per cent, determined on 3.000 g.

Sulphated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

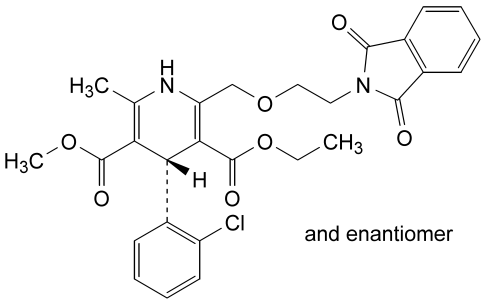
Injection: test solution (b), reference solution (a).

Calculate the percentage content of amlodipine besilate from the areas of the peaks and the declared content of $C_{26}H_{31}ClN_2O_8S$ in *amlodipine besilate CRS*.

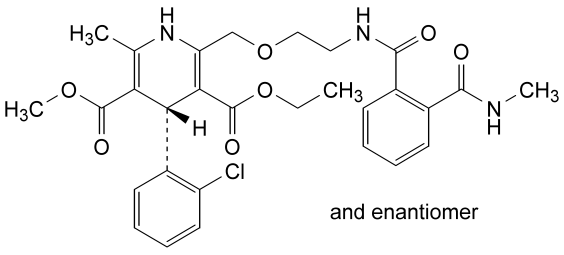
STORAGE

In an airtight container, protected from light.

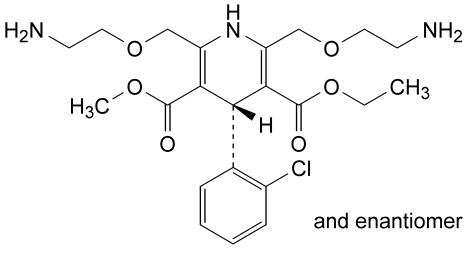
IMPURITIES



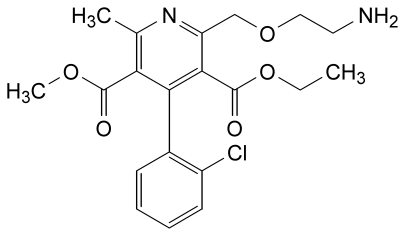
A. 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-2-[[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,



B. 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-6-methyl-2-[[2-[[2-(methylcarbamoyl)benzoyl]amino]ethoxy]methyl]-1,4-dihydropyridine-3,5-dicarboxylate,



C. ethyl methyl (4*RS*)-2,6-bis[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,



D. 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate.

01/2008:0877

AMMONIA SOLUTION, CONCENTRATED

Ammoniae solutio concentrata

NH_3 M_r 17.03

DEFINITION

Content: 25.0 per cent *m/m* to 30.0 per cent *m/m*.

CHARACTERS

Appearance: clear, colourless liquid, very caustic.

Solubility: miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Relative density (*2.2.5*): 0.892 to 0.910.

B. It is strongly alkaline (*2.2.4*).

C. To 0.5 ml add 5 ml of *water R*. Bubble air through the solution and lead the gaseous mixture obtained over the surface of a solution containing 1 ml of *0.1 M hydrochloric acid* and 0.05 ml of *methyl red solution R*. The colour changes from red to yellow. Add 1 ml of *sodium cobaltinitrite solution R*. A yellow precipitate is formed.

TESTS

Solution S. Evaporate 220 ml almost to dryness on a water-bath. Cool, add 1 ml of *dilute acetic acid R* and dilute to 20 ml with *distilled water R*.

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

To 2 ml add 8 ml of *water R*.

Oxidisable substances. Cautiously add, whilst cooling, 8.8 ml to 100 ml of *dilute sulphuric acid R*. Add 0.75 ml of *0.002 M potassium permanganate*. Allow to stand for 5 min. The solution remains faintly pink.

Pyridine and related substances: maximum 2 ppm, calculated as pyridine.

Measure the absorbance (*2.2.25*) at 252 nm using *water R* as the compensation liquid. The absorbance is not greater than 0.06.

Carbonates: maximum 60 ppm.

To 10 ml in a test-tube with a ground-glass neck add 10 ml of *calcium hydroxide solution R*. Stopper immediately and mix. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 ml of a 0.1 g/l solution of *anhydrous sodium carbonate R*.

Chlorides (*2.4.4*): maximum 1 ppm.

Dilute 5 ml of solution S to 15 ml with *water R*.

Sulphates (*2.4.13*): maximum 5 ppm.

Dilute 3 ml of solution S to 15 ml with *distilled water R*.

Iron (*2.4.9*): maximum 0.25 ppm.

Dilute 4 ml of solution S to 10 ml with *water R*.

Heavy metals (*2.4.8*): maximum 1 ppm.

Dilute 4 ml of solution S to 20 ml with *water R*. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (2 ppm Pb) R*.

Residue on evaporation: maximum 20 mg/l.

Evaporate 50 ml to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 1 mg.

ASSAY

Weigh accurately a flask with a ground-glass neck containing 50.0 ml of *1 M hydrochloric acid*. Add 2 ml of the substance to be examined and re-weigh. Add 0.1 ml of *methyl red solution R* as indicator. Titrate with *1 M sodium hydroxide* until the colour changes from red to yellow.

1 ml of *1 M hydrochloric acid* is equivalent to 17.03 mg of NH_3.

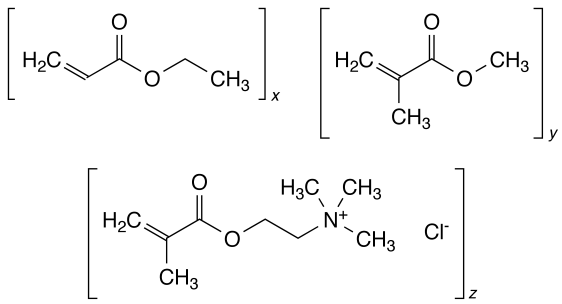
STORAGE

Protected from air, at a temperature not exceeding 20 °C.

01/2008:2081

AMMONIO METHACRYLATE COPOLYMER (TYPE A)

Ammonio methacrylatis copolymerum A



DEFINITION

Poly(ethyl propenoate-co-methyl 2-methylpropenoate-co-2-(trimethylammonio)ethyl 2-methylpropenoate) chloride having a mean relative molecular mass of about 150 000.

The ratio of ethyl propenoate groups to methyl 2-methylpropenoate groups to 2-(trimethylammonio)ethyl 2-methylpropenoate groups is about 1:2:0.2.

Content of ammonio methacrylate groups: 8.9 per cent to 12.3 per cent (dried substance).

CHARACTERS

Appearance: colourless to white or almost white granules or powder.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride giving clear to cloudy solutions. Due to the polymeric nature of the substance, a stirring time of up to 5 h may be necessary.