– *impurities B, E at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *sum of impurities other than D at 280 nm*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *sum of the impurities at 280 nm and impurity F at 254 nm*: maximum 0.7 per cent;
– *disregard limit at 280 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.000 g.

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

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.180 g in 50 ml of *acetic anhydride R* and add 10 ml of *anhydrous formic 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 20.56 mg of $C_8H_{12}ClNO_3$.

STORAGE

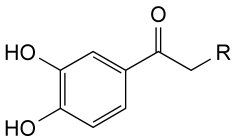
In an airtight container, or preferably in a sealed tube under vacuum or under an inert gas, protected from light.

IMPURITIES

Specified impurities: B, D, E, F.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, C, G.*

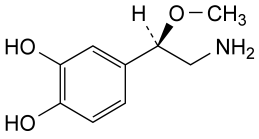
A. adrenaline,



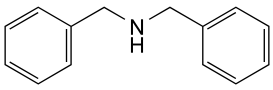
B. R = NH_2: 2-amino-1-(3,4-dihydroxyphenyl)ethanone (noradrenalone),

E. R = Cl: 2-chloro-1-(3,4-dihydroxyphenyl)ethanone,

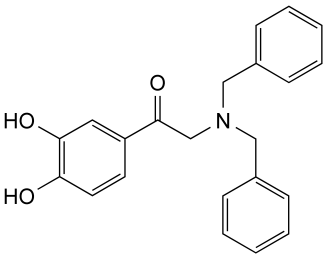
C. dopamine,



D. 4-[(1*R*)-2-amino-1-methoxyethyl]benzene-1,2-diol (noradrenaline methyl ether),



F. *N*-benzyl-1-phenylmethanamine,

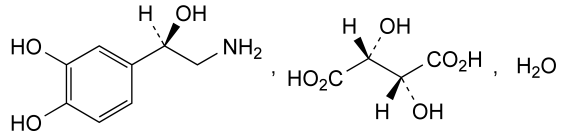


G. 2-(dibenzylamino)-1-(3,4-dihydroxyphenyl)ethanone.

01/2008:0285

NORADRENALINE TARTRATE

Noradrenalini tartras



$C_{12}H_{17}NO_9,H_2O$ M_r 337.3
[108341-18-0]

DEFINITION

(1*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 2 g in 20 ml of a 5 g/l solution of *sodium metabisulphite R* and make alkaline by addition of *ammonia R*. Keep in iced water for 1 h and filter. Reserve the filtrate for identification test C. Wash the precipitate with 3 quantities, each of 2 ml, of *water R*, then with 5 ml of *ethanol (96 per cent) R* and finally with 5 ml of *methylene chloride R* and dry *in vacuo* for 3 h. The specific optical rotation (*2.2.7*) of the precipitate (noradrenaline base) is – 44 to – 48, determined using a 20.0 g/l solution in *0.5 M hydrochloric acid*.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of noradrenaline base prepared as described in identification test A.

Comparison: use noradrenaline base prepared as described in identification test A from a suitable amount of *noradrenaline tartrate CRS*.

C. 0.2 ml of the filtrate obtained in identification test A gives reaction (b) of tartrates (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.2 g in *water R* and dilute to 10 ml with the same solvent. Examine the solution immediately.

Related substances. Liquid chromatography (*2.2.29*). *Protect the solutions from air. Remove oxygen from the mobile phases with nitrogen R immediately before use. Fill up the flasks.*

Test solution. Dissolve 0.20 g of the substance to be examined in mobile phase A and dilute to 50 ml with mobile phase A.

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

Reference solution (b). Dissolve 10 mg of the substance to be examined in 5 ml of *0.1 M hydrochloric acid.* To 1 ml of this solution add 0.1 ml of *strong hydrogen peroxide solution R* and expose to UV light at 254 nm for 90 min. Dilute to 10 ml with mobile phase A. The degradation of noradrenaline produces 2 peaks, one with a relative retention of about 1.2 (unidentified compound) and the other with a relative retention of about 1.5 (impurity B). Use this solution to identify the peak due to impurity B.

Reference solution (c). Dissolve 7.5 mg of *noradrenaline impurity D CRS* and 5 mg of *noradrenaline impurity E CRS* in mobile phase A and dilute to 100 ml with mobile phase A.

Reference solution (d). Dissolve 5 mg of *noradrenaline impurity F CRS* in mobile phase A and dilute to 10 ml with mobile phase A. To 1 ml of this solution, add 1 ml of reference solution (c) and dilute to 20 ml with mobile phase A.

Column:

- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *monolithic octadecylsilyl silica gel for chromatography R*;
- *temperature*: 25 °C.

Mobile phase:

- *mobile phase A*: dissolve 0.50 g of *sodium heptanesulphonate R* in *water for chromatography R* and dilute to 1000 ml with the same solvent; adjust to pH 2.2 with *phosphoric acid R*;
- *mobile phase B*: dissolve 0.25 g of *sodium heptanesulphonate R* in *water for chromatography R* and dilute to 500 ml with the same solvent; add 500 ml of *acetonitrile for chromatography R* and adjust the apparent pH to 2.4 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (ml/min)
0 - 2.0	98	2	1.5
2.0 - 17.0	98 → 70	2 → 30	1.5
17.0 - 24.0	70 → 50	30 → 50	1.5
24.0 - 24.1	50 → 0	50 → 100	1.5 → 4.0
24.1 - 28.0	0	100	4.0
28.0 - 28.1	0 → 98	100 → 2	4.0
28.1 - 30.0	98	2	4.0 → 1.5

Detection: spectrophotometer at 280 nm, except for impurity F: spectrophotometer at 254 nm.

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

Relative retention with reference to noradrenaline (retention time = about 3 min): impurity B = about 1.5; impurity D = about 2.8; impurity E = about 3.0; impurity F = about 6.9.

System suitability: reference solution (d):

- *resolution*: minimum 1.5 between the peaks due to impurities D and E.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.3; impurity E = 0.3; impurity F = 1.5;
- *impurity F at 254 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *impurities B, D, E at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *sum of the impurities at 280 nm and impurity F at 254 nm*: maximum 0.3 per cent;
- *disregard limit at 280 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): 4.5 per cent to 5.8 per cent, determined on 0.500 g.

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

ASSAY

Dissolve 0.300 g in 50 ml of *anhydrous acetic acid R*, heating gently if necessary. Titrate with *0.1 M perchloric acid* using 0.1 ml of *crystal violet solution R* as indicator, until a bluish-green colour is obtained.

1 ml of *0.1 M perchloric acid* is equivalent to 31.93 mg of $C_{12}H_{17}NO_9$.

STORAGE

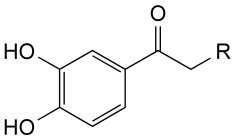
In an airtight container or preferably in a sealed tube under vacuum or under an inert gas, protected from light.

IMPURITIES

Specified impurities: *B, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034).* It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, C, G.*

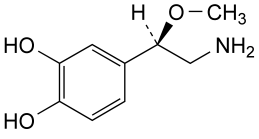
A. adrenaline,



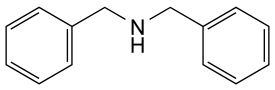
B. R = NH_2: 2-amino-1-(3,4-dihydroxyphenyl)ethanone (noradrenalone),

E. R = Cl: 2-chloro-1-(3,4-dihydroxyphenyl)ethanone,

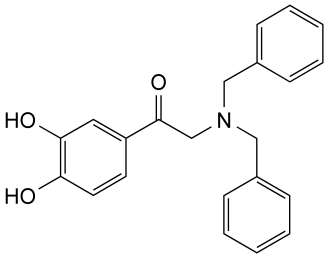
C. dopamine,



D. 4[(1*R*)-2-amino-1-methoxyethyl]benzene-1,2-diol (noradrenaline methyl ether),



F. *N*-benzyl-1-phenylmethanamine,

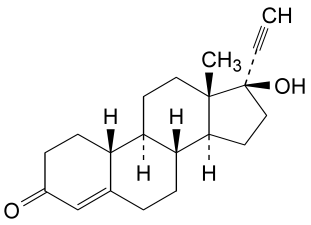


G. 2-(dibenzylamino)-1-(3,4-dihydroxyphenyl)ethanone.

01/2008:0234
corrected 6.0

NORETHISTERONE

Norethisteronum



$C_{20}H_{26}O_2$ M_r 298.4
[68-22-4]

DEFINITION

17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one.

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

CHARACTERS

Appearance: white or yellowish-white, crystalline powder.

Solubility: practically insoluble in water, soluble in methylene chloride, sparingly soluble in acetone and in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *norethisterone CRS*.

TESTS

Specific optical rotation (*2.2.7*): – 32.0 to – 37.0 (dried substance).

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

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in a mixture of 40 volumes of *water R* and 60 volumes of *acetonitrile R1* and dilute to 10.0 ml with the same mixture of solvents.

Reference solution (a). Dissolve 5 mg of *norethisterone for system suitability CRS* (containing impurities A, B, C, D, E, F, G and H) in a mixture of 40 volumes of *water R* and 60 volumes of *acetonitrile R1* and dilute to 2.0 ml with the same mixture of solvents.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with a mixture of 40 volumes of *water R* and 60 volumes of *acetonitrile R1*. Dilute 1.0 ml of this solution to 10.0 ml with a mixture of 40 volumes of *water R* and 60 volumes of *acetonitrile R1*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,

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

Mobile phase:

– *mobile phase A*: *water R*;

– *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	63	37
20 - 25	63 → 20	37 → 80
25 - 35	20	80
35 - 36	20 → 63	80 → 37
36 - 50	63	37

Flow rate: 1.0 ml/min.

Detection: variable wavelength spectrophotometer capable of operating at 254 nm and at 210 nm.

Injection: 20 µl.

Identification of impurities: use the chromatogram obtained with reference solution (a) and the chromatogram supplied with *norethisterone for system suitability CRS* to identify the peaks due to the impurities A, B, C, D, E, F, G and H.

Relative retention at 254 nm with reference to norethisterone (retention time = about 10 min): impurity H = about 0.3; impurity A = about 0.8; impurity B = about 0.9; impurity G = about 1.5; impurity C (at 210 nm) = about 1.6; impurity D (at 210 nm) = about 1.7; impurity E = about 2.3; impurity F = about 2.4.

System suitability: reference solution (a) at 254 nm:

– *resolution*: baseline separation between the peaks due to impurity B and norethisterone;

– *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits: spectrophotometer at 254 nm:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.5; impurity E = 0.7; impurity F = 1.4; impurity H = 1.7;

– *impurities E, G, H*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

– *impurities A, B, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);