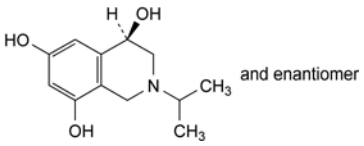
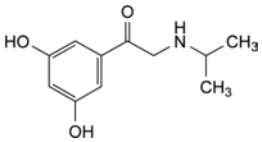
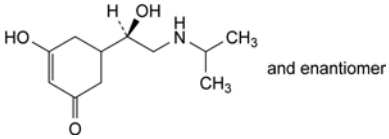


A. (4*RS*)-2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinoline-4,6,8-triol,



B. 1-(3,5-dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanone,



C. 3-hydroxy-5-[(1*RS*)-1-hydroxy-2-[(1-methylethyl)amino]-ethyl]cyclohex-2-enone.

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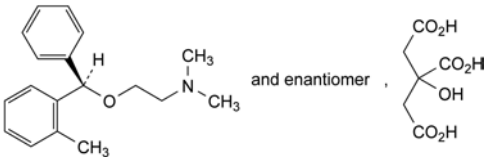
ORPHENADRINE CITRATE

Orphenadrini citras



$C_{24}H_{31}NO_8$ M_r 461.5
[4682-36-4]

DEFINITION

(*RS*)-*N*,*N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

mp: about 137 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *orphenadrine citrate CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 436 nm has a maximum of 0.050.

Dissolve 1.0 g in a 3.6 per cent *V/V* solution of *hydrochloric acid R* in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same acid solution.

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (a). Dissolve 30 mg of *orphenadrine citrate CRS* and 30 mg of *orphenadrine impurity E CRS* in 20 mL of *water R*. Add 1 mL of *concentrated ammonia R* and shake with 3 quantities, each of 5 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (b). Dissolve the contents of a vial of *orphenadrine for peak identification CRS* (containing impurities A, B, C, D and F) in 1.0 mL of *toluene R*.

Column:

– *size*: *l* = 60 m, Ø = 0.32 mm;
– *stationary phase*: *poly(dimethyl)(diphenyl)siloxane R* (film thickness 1.0 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 1 mL/min.

Split ratio: 1:25.

Temperature:

– *column*: 240 °C;
– *injection port and detector*: 290 °C.

Detection: flame ionisation.

Injection: 2 µL.

Run time: 1.3 times the retention time of orphenadrine.

Identification of impurities: use the chromatogram supplied with *orphenadrine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F. Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention with reference to orphenadrine (retention time = about 13 min): impurity B = about 0.5; impurity A = about 0.6; impurity D = about 0.8; impurity C = about 0.9; impurity E = about 0.98; impurity F = about 1.1.

System suitability: reference solution (a):

– *resolution*: minimum of 1.5 between the peaks due to impurity E and orphenadrine.

Limits:

– *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 per cent;
– *unspecified impurities*: for each impurity, not more than 0.10 per cent;
– *total*: maximum 1.0 per cent;
– *disregard limit*: 0.05 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution 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.

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

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

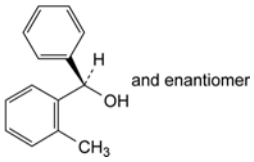
1 mL of *0.1 M perchloric acid* is equivalent to 46.15 mg of $C_{24}H_{31}NO_8$.

STORAGE

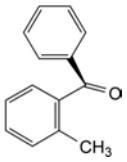
Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container, protected from light.

IMPURITIES

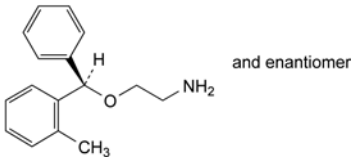
Specified impurities: *A, B, C, D, E, F*.



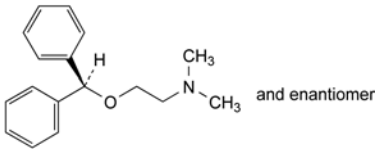
A. (*RS*)-(2-methylphenyl)phenylmethanol (2-methylbenzhydrol),



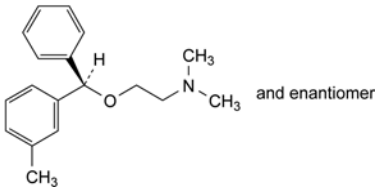
B. (2-methylphenyl)phenylmethanone (2-methylbenzophenone),



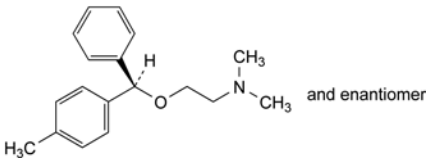
C. (*RS*)-2-[(2-methylphenyl)phenylmethoxy]ethanamine,



D. 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (diphenhydramine),



E. (*RS*)-*N*,*N*-dimethyl-2-[(3-methylphenyl)phenylmethoxy]ethanamine (*meta*-methylbenzyl isomer),



F. (*RS*)-*N*,*N*-dimethyl-2-[(4-methylphenyl)phenylmethoxy]ethanamine (*para*-methylbenzyl isomer).

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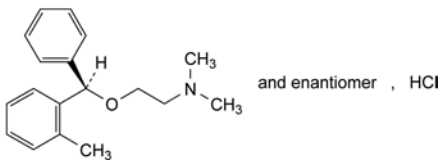
ORPHENADRINE HYDROCHLORIDE

Orphenadrini hydrochloridum



$C_{18}H_{24}ClNO$ M_r 305.9
[341-69-5]

DEFINITION

(*RS*)-*N*,*N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

mp: about 160 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *orphenadrine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 436 nm has a maximum of 0.050.

Dissolve 0.70 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Dissolve 0.300 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (a). Dissolve 20 mg of *orphenadrine hydrochloride CRS* and 20 mg of *orphenadrine impurity E CRS* in 20 mL of *water R*. Add 1 mL of *concentrated ammonia R* and shake with 3 quantities, each of 5 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (b). Dissolve the contents of a vial of *orphenadrine for peak identification CRS* (containing impurities A, B, C, D and F) in 1.0 mL of *toluene R*.

Column:
- *size*: *l* = 60 m, Ø = 0.32 mm;
- *stationary phase*: *poly(dimethyl)(diphenyl)siloxane R* (film thickness 1.0 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 1 mL/min.

Split ratio: 1:25.

Temperature:
- *column*: 240 °C;
- *injection port and detector*: 290 °C.

Detection: flame ionisation.

Injection: 2 µL.

Run time: 1.3 times the retention time of orphenadrine.

Identification of impurities: use the chromatogram supplied with *orphenadrine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F. Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention with reference to orphenadrine (retention time = about 13 min): impurity B = about 0.5; impurity A = about 0.6; impurity D = about 0.8; impurity C = about 0.9; impurity E = about 0.98; impurity F = about 1.1.

System suitability: reference solution (a):
- *resolution*: minimum 1.5 between the peaks due to impurity E and orphenadrine.

Limits:
- *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 per cent;
- *unspecified impurities*: for each impurity, not more than 0.10 per cent;