IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of dihydrocodeine hydrogen tartrate.*

B. To about 0.1 g add 1 mL of *sulfuric acid R* and 0.05 mL of *ferric chloride solution R1* and heat on a water-bath. A brownish-yellow colour develops. Add 0.05 mL of *dilute nitric acid R*. The colour does not become red.

C. To 1 mL of solution S (see Tests) add 5 mL of *picric acid solution R*. Heat on a water-bath until a clear solution is obtained. Allow to cool. A precipitate is formed. Filter, wash with 5 mL of *water R* and dry at 100-105 °C. The crystals melt (*2.2.14*) at 220 °C to 223 °C.

D. It gives reaction (b) of tartrates (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

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

pH (*2.2.3*): 3.2 to 4.2 for solution S.

Specific optical rotation (*2.2.7*): – 70.5 to – 73.5 (anhydrous substance).

Dilute 10.0 mL of solution S to 20.0 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 2.0 mg of *codeine phosphate R* in 2.0 mL of the test solution and dilute to 25.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 200 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

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

Mobile phase: to 1.0 g of *sodium heptanesulfonate R*, add 10.0 mL of *glacial acetic acid R* and 4.0 mL of a solution of 5.0 mL of *triethylamine R* diluted to 25.0 mL with a mixture of equal volumes of *water R* and *acetonitrile R*. Add 170 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 284 nm.

Injection: 20 µL.

Run time: 5 times the retention time of dihydrocodeine.

Retention time: dihydrocodeine = about 14 min.

System suitability: reference solution (a):

– *resolution*: minimum of 2 between the peaks due to dihydrocodeine and to impurity A.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *any other peak*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent); disregard any peak due to tartaric acid (relative retention with reference to dihydrocodeine = about 0.25),

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): maximum 0.7 per cent, determined on 1.00 g.

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

ASSAY

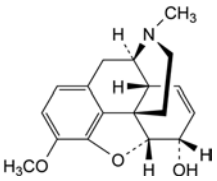
Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 45.15 mg of $C_{22}H_{29}NO_9$.

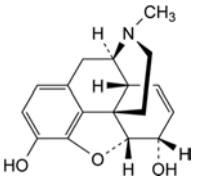
STORAGE

Protected from light.

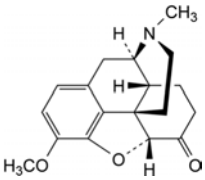
IMPURITIES



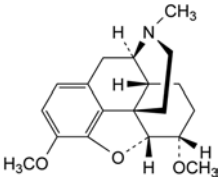
A. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (codeine),



B. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol (morphine),



C. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone),

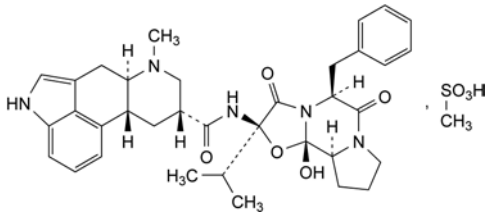


D. 4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (tetrahydrothebaine).

01/2008:1416
corrected 7.0

DIHYDROERGOCRISTINE MESILATE

Dihydroergocristini mesilas



$C_{36}H_{45}N_5O_8S$ M_r 708

[24730-10-7]

DEFINITION

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxo-octahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulfonate.

Content: 98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

Appearance: white or almost white, fine crystalline powder.

Solubility: slightly soluble in water, soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *dihydroergocristine mesilate CRS*.

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

Test solution. Dissolve 0.10 g of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

Reference solution. Dissolve 0.10 g of *dihydroergocristine mesilate CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

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

Mobile phase: *concentrated ammonia R, dimethylformamide R, ether R* (2:15:85 *V/V/V*).

Application: 5 µL.

Development: over 2/3 of the plate protected from light.

Drying: in a current of cold air for 5 min.

Detection: spray with *dimethylaminobenzaldehyde solution R7* and dry in a current of hot air for 2 min.

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

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

Test solution. Dissolve 0.20 g of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

Reference solution. Dissolve 0.20 g of *methanesulfonic acid R* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents. Dilute 1 mL of the solution to 10 mL with a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R*.

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

Mobile phase: *water R, concentrated ammonia R, butanol R, acetone R* (5:10:20:65 *V/V/V/V*).

Application: 10 µL.

Development: over a path of 10 cm protected from light.

Drying: in a current of cold air for not more than 1 min.

Detection: spray with a 1 g/L solution of *bromocresol purple R* in *methanol R*, adjusting the colour to violet-red with one drop of *dilute ammonia R1* and dry the plate in a current of hot air at 100 °C.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 0.50 g in *methanol R* and dilute to 25.0 mL with the same solvent.

pH (*2.2.3*): 4.0 to 5.0.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*): – 37 to – 43 (dried substance).

Dissolve 0.250 g in *anhydrous pyridine R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test and preparation of the solutions protected from bright light.*

Test solution. Dissolve 75.0 mg of the substance to be examined in 10 mL of *acetonitrile R*. Add 10 mL of a 1.0 g/L solution of *phosphoric acid R* and dilute to 50.0 mL with *water R*.

Reference solution. Dissolve 20.0 mg of *codergocrine mesilate CRS* in 10 mL of *acetonitrile R*. Add 10 mL of a 1.0 g/L solution of *phosphoric acid R* and dilute to 50.0 mL with *water R*. Dilute 6.0 mL of the solution to 50.0 mL with a mixture of 20 volumes of *acetonitrile R*, 20 volumes of a 1.0 g/L solution of *phosphoric acid R* and 60 volumes of *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase:

– *mobile phase A*: mix 100 volumes of *acetonitrile R* with 900 volumes of *water R* and add 10 volumes of *triethylamine R*,
– *mobile phase B*: mix 100 volumes of *water R* with 900 volumes of *acetonitrile R* and add 10 volumes of *triethylamine R*.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	75	25
5 - 20	75 → 25	25 → 75

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 10 µL.

Relative retention with reference to dihydroergocristine (retention time = about 13.7 min): impurity F = about 0.8; impurity H = about 0.9; impurity I = about 1.02.

System suitability: reference solution:

– the chromatogram shows 4 peaks,
– *resolution*: minimum 1 between the peaks corresponding to dihydroergocristine and impurity I.

Limits:

– *any impurity*: not more than the area of the peak corresponding to dihydroergocristine in the chromatogram obtained with the reference solution (1 per cent),
– *total*: not more than twice the area of the peak corresponding to dihydroergocristine in the chromatogram obtained with the reference solution (2 per cent),

Monographs D-E

– *disregard limit*: 0.1 times the area of the peak corresponding to dihydroergocristine in the chromatogram obtained with the reference solution (0.1 per cent).

Loss on drying (*2.2.32*): maximum 3.0 per cent, determined on 0.500 g by drying under high vacuum at 80 °C.

ASSAY

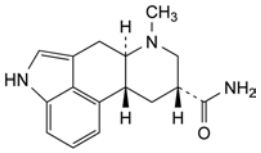
Dissolve 0.300 g in 60 mL of *pyridine R*. Pass a stream of *nitrogen R* over the surface of the solution and titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Note the volume used at the second point of inflexion.

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 35.39 mg of $C_{36}H_{45}N_5O_8S$.

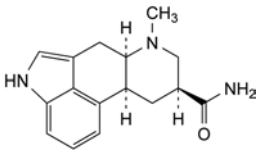
STORAGE

Store protected from light.

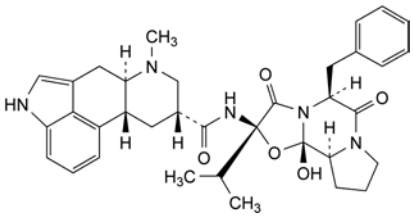
IMPURITIES



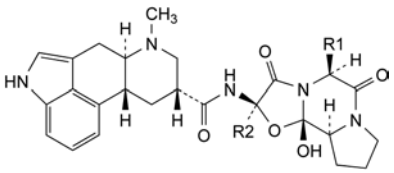
A. (6a*R*,9*R*,10a*R*)-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (6-methylergoline-8β-carboxamide),



B. (6a*R*,9*S*,10a*S*)-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (6-methylisoergoline-8α-carboxamide),



C. (6a*R*,9*R*,10a*R*)-*N*-[(2*S*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (2′-epidihydroergocristine),



D. R1 = $CH(CH_3)_2$, R2 = CH_3: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-methyl-5-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergosine),

E. R1 = CH_2-C_6H_5, R2 = CH_3: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline- 9-carboxamide (dihydroergotamine),

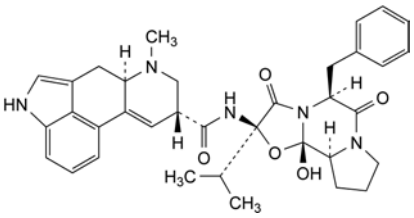
F. R1 = R2 = $CH(CH_3)_2$: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)10b-hydroxy-2,5-bis(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergocornine),

G. R1 = CH_2-C_6H_5, R2 = CH_2-CH_3: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-2-ethyl-10b-hydroxy-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergostine),

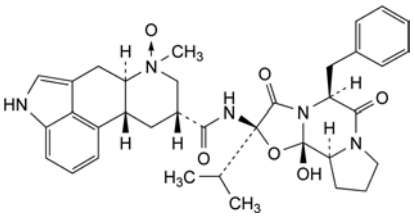
H. R1 = CH_2-$CH(CH_3)_2$, R2 = $CH(CH_3)_2$: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (α-dihydroergocryptine),

I. R1 = C*H(CH_3)-CH_2-CH_3, R2 = $CH(CH_3)_2$: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-[(1*RS*-1-methylpropyl]-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (β-dihydroergocryptine or epicriptine),

J. R1 = CH_2-C_6H_5, R2 = C*H(CH_3)-CH_2-CH_3: (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-[(1*RS*)-1-methylpropyl]-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergosedmine),



K. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergocristine),

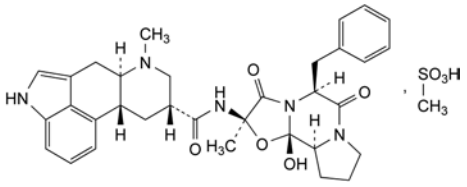


L. (6a*R*,7*RS*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide 7-oxide (dihydroergocristine 6-oxide).

04/2009:0551

DIHYDROERGOTAMINE MESILATE

Dihydroergotamini mesilas



$C_{34}H_{41}N_5O_8S$ M_r 680
[6190-39-2]

DEFINITION

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulfonate.

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

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

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

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 5.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent.

Spectral range: 250-350 nm.

Absorption maxima: at 281 nm and 291 nm.

Shoulder: at 275 nm.

Absorbance: negligible above 320 nm.

Specific absorbance at the absorption maximum at 281 nm: 95 to 105 (dried substance).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *dihydroergotamine mesilate CRS.*

C. Thin-layer chromatography (*2.2.27*). *Prepare the reference solution and the test solution immediately before use.*

Solvent mixture: *methanol R, methylene chloride R* (10:90 *V/V*).

Test solution. Dissolve 5 mg of the substance to be examined in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Reference solution. Dissolve 5 mg of *dihydroergotamine mesilate CRS* in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Plate: *TLC silica gel G plate R.*

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R, methylene chloride R* (1:6:50:50 *V/V/V/V*).

Application: 5 µL.

Development: protected from light, over a path of 15 cm; dry in a current of cold air for not longer than 1 min and repeat the development protected from light over a path of 15 cm using a freshly prepared amount of the mobile phase.

Drying: in a current of cold air.

Detection: spray abundantly with *dimethylaminobenzaldehyde solution R7* and dry in a current of hot air for about 2 min.

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

D. To 0.1 g of the substance to be examined, add 5 mL of *dilute hydrochloric acid R* and shake for about 5 min. Filter, then add 1 mL of *barium chloride solution R1*. The filtrate remains clear. Mix 0.1 g of the substance to be examined with 0.4 g of powdered *sodium hydroxide R*, heat to fusion and continue to heat for 1 min. Cool, add 5 mL of *water R*, boil and filter. Acidify the filtrate with *hydrochloric acid R1* and filter again. The filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 or BY_7 (*2.2.2, Method II*).

Dissolve 0.10 g in a mixture of 0.1 mL of a 70 g/L solution of *methanesulfonic acid R* and 50 mL of *water R*.

pH (*2.2.3*): 4.4 to 5.4.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Specific optical rotation (*2.2.7*): – 42 to – 47 (dried substance).

Dissolve 0.250 g in *anhydrous pyridine R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture: *acetonitrile R, water R* (50:50 *V/V*).

Test solution. Dissolve 70 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dissolve 7 mg of the substance to be examined and 6.8 mg of *ergotamine tartrate CRS* (impurity A) (equivalent to 7 mg of ergotamine mesilate) in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 5 mL of this solution to 10 mL with the solvent mixture.

Reference solution (c). Dissolve 5 mg of *dihydroergotamine for peak identification CRS* (containing impurities A, B, C, D and E) in the solvent mixture, add 100 µL of *dilute sulfuric acid R* and dilute to 5 mL with the solvent mixture.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
– *temperature*: 25 °C.

Mobile phase:

– *mobile phase A*: 3 g/L solution of *sodium heptanesulfonate monohydrate R* adjusted to pH 2.0 with *phosphoric acid R*;
– *mobile phase B*: mobile phase A, *acetonitrile for chromatography R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	58 → 40	42 → 60

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 220 nm.