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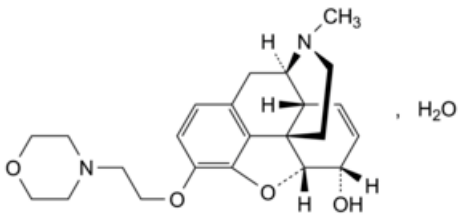
Pholcodine Monohydrate

General Notices

Pholcodine

(Ph. Eur. monograph 0522)



$C_{23}H_{30}N_2O_4,H_2O$ 416.5 *6254-99-5*

Action and use

Opioid receptor agonist; cough suppressant.

Preparations

Pholcodine Linctus

Strong Pholcodine Linctus

Ph Eur

DEFINITION

17-Methyl-3-[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan-6α-ol monohydrate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Sparingly soluble in water, freely soluble in acetone and in ethanol (96 per cent). It dissolves in dilute mineral acids.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pholcodine CRS*.

TESTS

Specific optical rotation (*2.2.7*)

-98 to -94 (dried substance).

Dissolve 1.000 g in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

0.02 M phosphate buffer solution To 80.0 mL of *0.2 M sodium hydroxide* add 100.0 mL of *0.2 M potassium dihydrogen phosphate R* and dilute to 1.0 L with *water R*.

Solvent mixture Dilute 80 mL of *acetonitrile R* to 1 L with the 0.02 M phosphate buffer solution.

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *codeine R* (impurity B) in the solvent mixture and dilute to 10 mL with the solvent mixture. To 0.5 mL of this solution add 0.5 mL of the test solution and dilute to 50 mL with the solvent mixture.

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

Reference solution (c) Dissolve 5 mg of *pholcodine for peak identification CRS* (containing impurities A, B and D) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *pholcodine for impurity G identification CRS* in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core phenylhexylsilyl silica gel for chromatography R* (2.6 µm);

— *temperature*: 35 °C.

Mobile phase To 50 mL of *tetrahydrofuran for chromatography R* add 75 mL of *acetonitrile R* and dilute to 1000 mL with the 0.02 M phosphate buffer solution; adjust to pH 7.9 ± 0.05 with *0.2 M sodium hydroxide*; the pH must not exceed 8.0.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 20 µL.

Run time 5 times the retention time of pholcodine.

Identification of impurities Use the chromatogram supplied with *pholcodine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to pholcodine (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.8; impurity D = about 2.3; impurity G = about 4.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and pholcodine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 0.5;

— *impurities A, B, D*: 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);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 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 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

3.9 per cent to 4.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

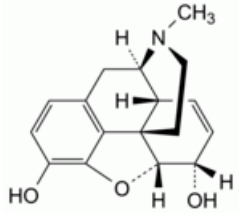
Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*, warming gently. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 19.93 mg of $C_{23}H_{30}N_2O_4$.

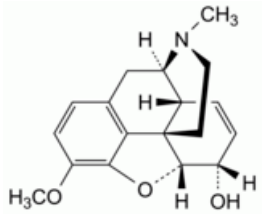
IMPURITIES

Specified impurities *A, B, D, G*.

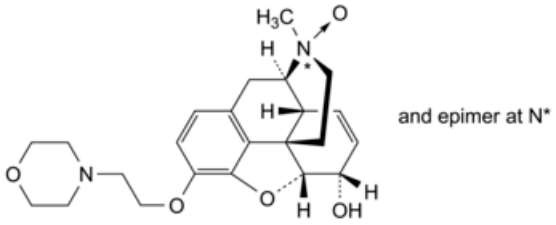
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *C, E, F*.



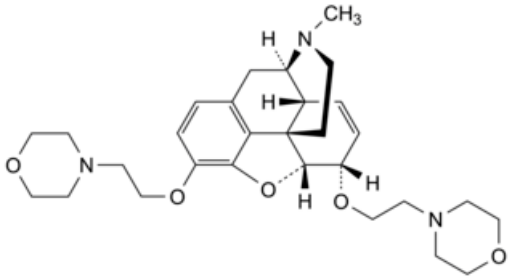
A. 17-methyl-7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol (morphine),



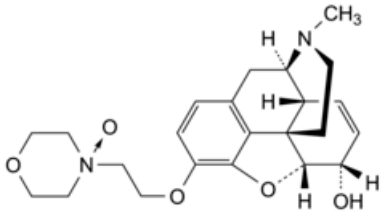
B. 3-methoxy-17-methyl-7,8-didehydro-4,5α-epoxymorphinan-6α-ol (codeine),



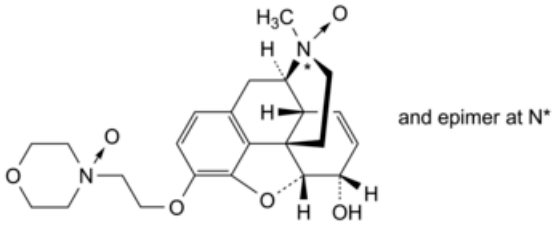
C. (17*RS*)-6α-hydroxy-17-methyl-3-[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan 17-oxide (pholcodine *N*-oxide),



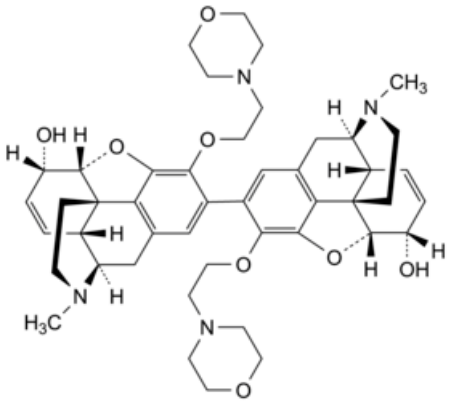
D. 17-methyl-3,6α-bis[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan,



E. 4-[2-[(6α-hydroxy-17-methyl-7,8-didehydro-4,5α-epoxymorphinan-3-yl)oxy]ethyl]morpholine 4-oxide (pholcodine *N*′-oxide),



F. (17*RS*)-6α-hydroxy-17-methyl-3-[2-(4-oxidomorpholin-4-ium-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan 17-oxide (pholcodine *N*,*N*′-dioxide),



G. 17,17'-dimethyl-3,3'-bis[2-(morpholin-4-yl)ethoxy]-7,7',8,8'-tetradehydro-4,5α:4',5'α-diepoxybimorphinan-6α,6'α-diol (pholcodine dimer).

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