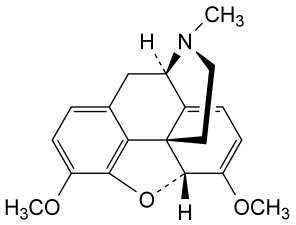
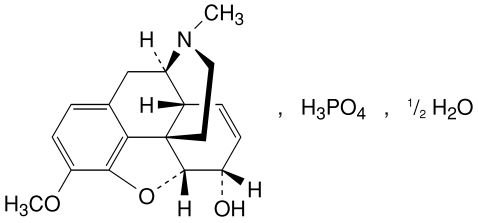


G. 6,7,8,14-tetradehydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan (thebaine).

01/2008:0074
corrected 6.0

CODEINE PHOSPHATE HEMIHYDRATE

Codeini phosphas hemihydricus



$C_{18}H_{24}NO_7P,{}^1/_2H_2O$ M_r 406.4
[41444-62-6]

DEFINITION

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate hemihydrate.

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

CHARACTERS

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

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

IDENTIFICATION

First identification: B, E, F.

Second identification: A, C, D, E, F, G.

A. Dilute 1.0 ml of solution S (see Tests) to 100.0 ml with *water R*. To 25.0 ml of this solution add 25 ml of *water R* then 10 ml of *1 M sodium hydroxide* and dilute to 100.0 ml with *water R*. Examined between 250 nm and 350 nm (*2.2.25*), the solution shows only 1 absorption maximum, at 284 nm. The specific absorbance at the absorption maximum is about 38 (dried substance).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dissolve 0.20 g in 4 ml of *water R*. Add 1 ml of a mixture of equal volumes of *strong sodium hydroxide solution R* and *water R* and initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod and cooling in iced water. Wash the precipitate with *water R* and dry at 100-105 °C. Examine the dried precipitate prepared as discs using *potassium bromide R*.

Comparison: *Ph. Eur. reference spectrum of codeine.*

C. Dissolve 0.20 g in 4 ml of *water R*. Add 1 ml of a mixture of equal volumes of *strong sodium hydroxide solution R* and *water R* and initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod and cooling in iced water. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at 155 °C to 159 °C.

D. To about 10 mg add 1 ml of *sulphuric acid R* and 0.05 ml of *ferric chloride solution R2* and heat on a water-bath. A blue colour develops. Add 0.05 ml of *nitric acid R*. The colour changes to red.

E. It complies with the test for loss on drying (see Tests).

F. Solution S gives reaction (a) of phosphates (*2.3.1*).

G. It gives the reaction of alkaloids (*2.3.1*).

TESTS

Solution S. Dissolve 1.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 25.0 ml with the same solvent.

pH (*2.2.3*): 4.0 to 5.0 for solution S.

Specific optical rotation (*2.2.7*): – 98 to – 102 (dried substance).

Dilute 5.0 ml of solution S to 10.0 ml with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined and 0.100 g of *sodium octanesulphonate R* in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *codeine impurity A CRS* in the mobile phase and dilute to 5.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 5.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (d). To 0.25 ml of the test solution add 2.5 ml of reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 1.08 g of *sodium octanesulphonate R* in a mixture of 20 ml of *glacial acetic acid R* and 250 ml of *acetonitrile R* and dilute to 1000 ml with *water R*.

Flow rate: 2 ml/min.

Detection: spectrophotometer at 245 nm.

Injection: 10 µl.

Run time: 10 times the retention time of codeine.

Relative retention with reference to codeine (retention time = about 6 min): impurity B = about 0.6; impurity E = about 0.7; impurity A = about 2.0; impurity C = about 2.3; impurity D = about 3.6.

System suitability: reference solution (d):

– *resolution*: minimum 3 between the peaks due to codeine and impurity A.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.25,
– *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),
– *impurities B, C, D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent),

- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent),
- *sum of impurities other than A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent),
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Sulphates (*2.4.13*): maximum 0.1 per cent.

Dilute 5 ml of solution S to 20 ml with *distilled water R*. 15 ml of the solution complies with the limit test for sulphates.

Loss on drying (*2.2.32*): 1.5 per cent to 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.350 g in a mixture of 10 ml of *anhydrous acetic acid R* and 20 ml of *dioxan R*. Titrate with *0.1 M perchloric acid* using 0.05 ml of *crystal violet solution R* as indicator.

1 ml of *0.1 M perchloric acid* is equivalent to 39.74 mg of $C_{18}H_{24}NO_7P$.

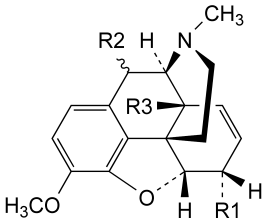
STORAGE

Protected from light.

IMPURITIES

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

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*): *F, G.*

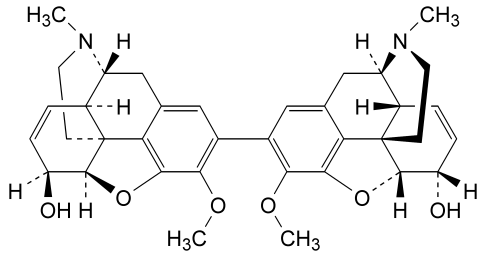


A. R1 = OCH_3, R2 = R3 = H: 7,8-didehydro-4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (methylcodeine),

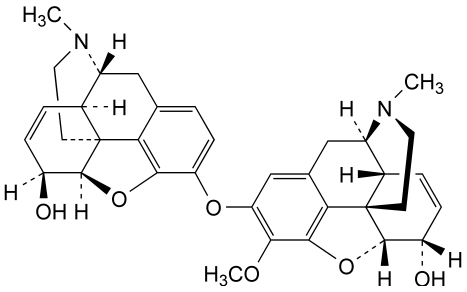
E. R1 = R2 = OH, R3 = H: 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α,10-diol,

F. R1 = R3 = OH, R2 = H: 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α,14-diol,

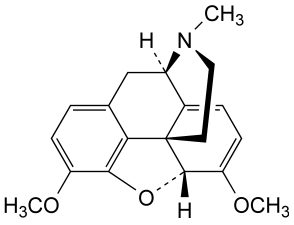
B. morphine,



C. 7,7′,8,8′-tetradehydro-4,5α:4′,5′α-diepoxy-3,3′-dimethoxy-17,17′-dimethyl-2,2′-bimorphinanyl-6α,6′α-diol (codeine dimer),



D. 7,8-didehydro-2-[(7,8-didehydro-4,5α-epoxy-6α-hydroxy-17-methylmorphinan-3-yl)oxy]-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (3-*O*-(codein-2-yl)morphine),

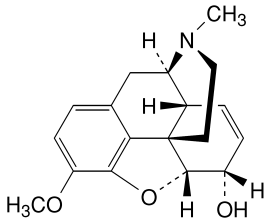


G. 6,7,8,14-tetradehydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan (thebaine).

01/2008:0075
corrected 6.0

CODEINE PHOSPHATE SESQUIHYDRATE

Codeini phosphas sesquihydricus



, H_3PO_4 , $1\frac{1}{2}$ H_2O

$C_{18}H_{24}NO_7P,1\frac{1}{2}H_2O$ M_r 424.4
[5913-76-8]

DEFINITION

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate sesquihydrate.

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

CHARACTERS

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

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

IDENTIFICATION

First identification: B, E, F.

Second identification: A, C, D, E, F, G.

A. Dilute 1.0 ml of solution S (see Tests) to 100.0 ml with *water R*. To 25.0 ml of this solution add 25 ml of *water R* then 10 ml of *1 M sodium hydroxide* and dilute to 100.0 ml with *water R*. Examined between 250 nm and 350 nm (*2.2.25*), the solution shows only 1 absorption maximum, at 284 nm. The specific absorbance at the absorption maximum is about 38 (dried substance).

B. Infrared absorption spectrophotometry (*2.2.24*).