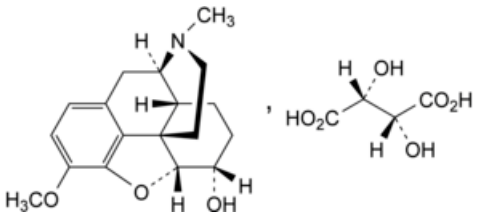
Edition: BP 2025 (Ph. Eur. 11.6 update)

Dihydrocodeine Tartrate

General Notices

(Dihydrocodeine Hydrogen Tartrate, Ph. Eur. monograph 1776)



$C_{22}H_{29}NO_9$ 451.5 *5965-13-9*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Co-dydramol Tablets

Dihydrocodeine Injection

Dihydrocodeine Oral Solution

Dihydrocodeine Tablets

Dihydrocodeine Prolonged-release Tablets

Ph Eur

DEFINITION

4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

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, sparingly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

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

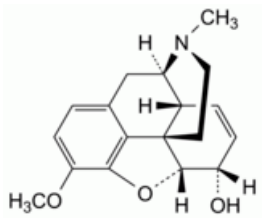
Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

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

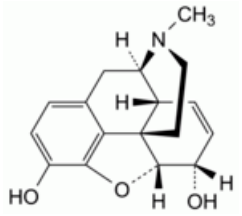
STORAGE

Protected from light.

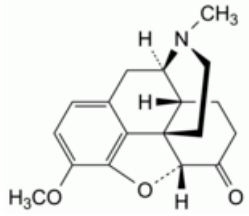
IMPURITIES



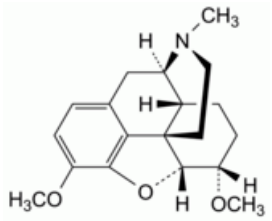
A. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (codeine),



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).

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