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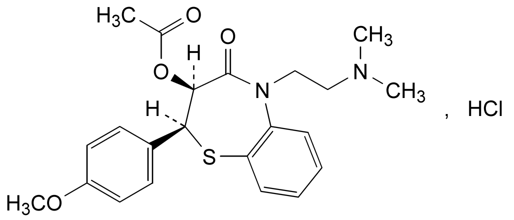
DILTIAZEM HYDROCHLORIDE

Diltiazemi hydrochloridum



$C_{22}H_{27}ClN_2O_4S$ M_r 451.0
[33286-22-5]

DEFINITION

Hydrochloride of (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.

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, in methanol and in methylene chloride, slightly soluble in anhydrous ethanol.

mp: about 213 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *diltiazem hydrochloride CRS.*

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

Test solution. Dissolve 0.10 g of the substance to be examined in *methylene chloride R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 0.10 g of *diltiazem hydrochloride CRS* in *methylene chloride R* and dilute to 10 ml with the same solvent.

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

Mobile phase: *acetic acid R, water R, methylene chloride R, anhydrous ethanol R* (1:3:10:12 *V/V/V/V*).

Application: 10 µl.

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

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

C. Dissolve 50 mg in 5 ml of *water R*. Add 1 ml of *ammonium reineckate solution R*. A pink precipitate is produced.

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

TESTS

Solution S. Dissolve 1.00 g in *carbon-dioxide free water R* and dilute to 20.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.3 to 5.3.

Dilute 2.0 ml of solution S to 10.0 ml with *carbon dioxide-free water R.*

Specific optical rotation (*2.2.7*): + 115 to + 120 (dried substance).

Dilute 5.0 ml of solution S to 25.0 ml with *water R.*

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 200.0 ml with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *diltiazem hydrochloride CRS* in the mobile phase and dilute to 200.0 ml with the mobile phase.

Reference solution (b). Dissolve 3 mg of *diltiazem impurity A CRS* in the mobile phase and dilute to 10 ml with the mobile phase. To 1 ml of this solution add 1.2 ml of reference solution (a) and dilute to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 0.3 ml of the test solution to 100.0 ml with the mobile phase.

Column:

- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase: mix 5 volumes of *anhydrous ethanol R*, 25 volumes of *acetonitrile R* and 70 volumes of a solution containing 6.8 g/l of *potassium dihydrogen phosphate R* and 0.1 ml/l of *N,N-dimethyloctylamine R*, adjusted to pH 4.5 using *dilute phosphoric acid R.*

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µl.

Run time: 5 times the retention time of diltiazem.

System suitability: reference solution (b):

- *resolution*: minimum 4.0 between the peaks due to impurity A and diltiazem;
- *symmetry factor*: maximum 2.0 for the peaks due to impurity A and diltiazem.
- if necessary, adjust the concentration of *N,N*-dimethyloctylamine in the mobile phase.

Limits:

- *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);
- *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (c).

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

Dissolve 2.0 g in *water R* and dilute to 20.0 ml with the same solvent. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 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 2 h.

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

ASSAY

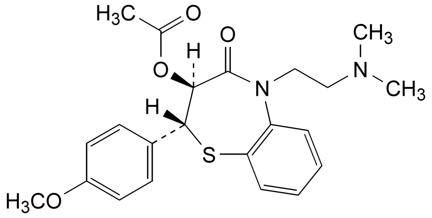
Dissolve 0.400 g in a mixture of 2 ml of *anhydrous formic acid R* and 60 ml of *acetic anhydride R* and titrate with *0.1 M perchloric acid,* determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 45.1 mg of $C_{22}H_{27}ClN_2O_4S$.

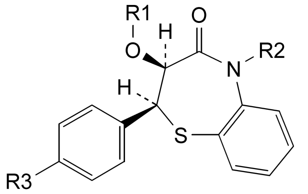
STORAGE

In an airtight container, protected from light.

IMPURITIES



A. (2*R*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



B. R1 = CO-CH_3, R2 = H, R3 = OCH_3: (2*S*,3*S*)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,

C. R1 = CO-CH_3, R2 = CH_2-CH_2-N$(CH_3)_2$, R3 = OH: (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,

D. R1 = CO-CH_3, R2 = CH_2-CH_2-NH-CH_3, R3 = OCH_3: (2*S*,3*S*)-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,

E. R1 = R2 = H, R3 = OCH_3: (2*S*,3*S*)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one,

F. R1 = H, R2 = CH_2-CH_2-N$(CH_3)_2$, R3 = OCH_3: (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one.

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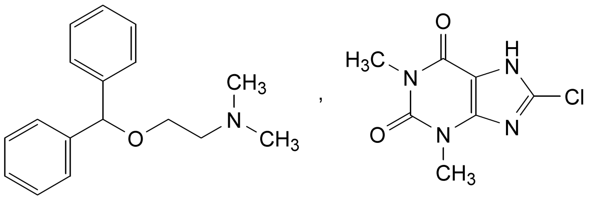
DIMENHYDRINATE

Dimenhydrinatum



$C_{24}H_{28}ClN_5O_3$ M_r 470.0
[523-87-5]

DEFINITION

Dimenhydrinate contains not less than 53.0 per cent and not more than 55.5 per cent of diphenhydramine [2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine, $C_{17}H_{21}NO$, M_r 255.4] and not less than 44.0 per cent and not more than 46.5 per cent of 8-chlorotheophylline (8-chloro-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione, $C_7H_7ClN_4O_2$, M_r 214.6), both calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, slightly soluble in water, freely soluble in alcohol.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 102 °C to 106 °C.

B. Dissolve 0.1 g in a mixture of 3 ml of *water R* and 3 ml of *alcohol R*, add 6 ml of *water R* and 1 ml of *dilute hydrochloric acid R* and cool in iced water for 30 min, scratching the wall of the tube with a glass rod if necessary to initiate crystallisation. Dissolve about 10 mg of the precipitate obtained in 1 ml of *hydrochloric acid R*, add 0.1 g of *potassium chlorate R* and evaporate to dryness in a porcelain dish. A reddish residue is obtained which becomes violet-red when exposed to ammonia vapour.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *dimenhydrinate CRS*.

D. Dissolve 0.2 g in 10 ml of *alcohol R*. Add 10 ml of *picric acid solution R* and initiate crystallisation by scratching the wall of the tube with a glass rod. The precipitate, washed with *water R* and dried at 100 °C to 105 °C, melts (*2.2.14*) at 130 °C to 134 °C.

TESTS

Appearance of solution. Dissolve 1.0 g in *alcohol R* and dilute to 20 ml with the same solvent. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*). To 0.4 g add 20 ml of *carbon dioxide-free water R*, shake for 2 min and filter. The pH of the filtrate is 7.1 to 7.6.

Theophylline and substances related to diphenhydramine. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 0.40 g of the substance to be examined in *methylene chloride R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 20 mg of *theophylline R* in *methylene chloride R* and dilute to 100 ml with the same solvent.

Reference solution (b). Dilute 5 ml of the test solution to 100 ml with *methylene chloride R*. Dilute 10 ml of this solution to 100 ml with *methylene chloride R*.

Apply separately to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 9 volumes of *methanol R* and 90 volumes of *methylene chloride R*. Dry the plate in a current of cold air and examine in ultraviolet light at 254 nm. Any spot corresponding to theophylline in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent). Spray with *potassium iodobismuthate solution R*. Allow the plate to dry in air and spray with *dilute hydrogen peroxide solution R*. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any spot extending from the starting point to an R_F of about 0.1.