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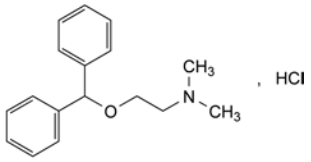
DIPHENHYDRAMINE HYDROCHLORIDE

Diphenhydramini hydrochloridum



$C_{17}H_{22}ClNO$ M_r 291.8
[147-24-0]

DEFINITION

2-(Diphenylmethoxy)-*N*,*N*-dimethylethanamine hydrochloride.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, freely soluble in alcohol.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 168 °C to 172 °C.

B. Dissolve 50 mg in *alcohol R* and dilute to 100.0 mL with the same solvent. Examined between 230 nm and 350 nm, the solution shows 3 absorption maxima (*2.2.25*), at 253 nm, 258 nm and 264 nm. The ratio of the absorbance measured at the maximum at 258 nm to that measured at the maximum at 253 nm is 1.1 to 1.3. The ratio of the absorbance measured at the maximum at 258 nm to that measured at the maximum at 264 nm is 1.2 to 1.4.

C. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: discs.
Comparison: *diphenhydramine hydrochloride CRS*.

D. It gives the reactions of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S and a fivefold dilution of solution S are clear (*2.2.1*). Solution S is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S add 0.15 mL of *methyl red solution R* and 0.25 mL of *0.01 M hydrochloric acid*. The solution is pink. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 70 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *diphenhydramine impurity A CRS* and 5 mg of *diphenylmethanol R* in the mobile phase and dilute to 10.0 mL with the mobile phase. To 2.0 mL of this solution add 1.5 mL of the test solution and dilute to 10.0 mL with the mobile phase.

Column:

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

Mobile phase: mix 35 volumes of *acetonitrile R* and 65 volumes of a 5.4 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 using *phosphoric acid R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 7 times the retention time of diphenhydramine.

Relative retention with reference to diphenhydramine (retention time = about 6 min): impurity A = about 0.9; impurity B = about 1.5; impurity C = about 1.8; impurity D = about 2.6; impurity E = about 5.1.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to diphenhydramine and to impurity A.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.7,
– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *any other impurity*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),
– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 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 0.250 g in 50 mL of *alcohol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

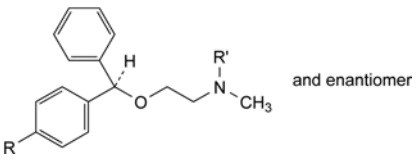
1 mL of *0.1 M sodium hydroxide* is equivalent to 29.18 mg of $C_{17}H_{22}ClNO$.

STORAGE

Protected from light.

IMPURITIES

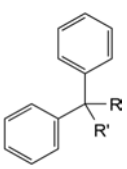
Specified impurities: A, B, C, D, E.



A. R = R′ = H: 2-(diphenylmethoxy)-*N*-methylethanamine,

B. R = R′ = CH_3: 2-[(*RS*)-(4-methylphenyl)phenylmethoxy]-*N*,*N*-dimethylethanamine,

C. R = Br, R′ = CH_3: 2-[(*RS*)-(4-bromophenyl)phenylmethoxy]-*N*,*N*-dimethylethanamine,



D. R = OH, R′ = H: diphenylmethanol (benzhydrol),

E. R + R′ = O: diphenylmethanone (benzophenone).

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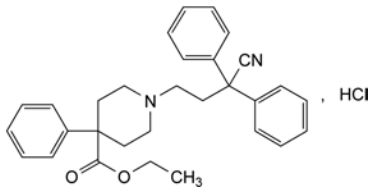
DIPHENOXYLATE HYDROCHLORIDE

Diphenoxylati hydrochloridum



$C_{30}H_{33}ClN_2O_2$ M_r 489.1
[3810-80-8]

DEFINITION

Diphenoxylate hydrochloride contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol.

It melts at about 220 °C, with decomposition.

IDENTIFICATION

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the *Ph. Eur. reference spectrum of diphenoxylate hydrochloride*.

B. Dissolve about 30 mg in 5 mL of *methanol R*. Add 0.25 mL of *nitric acid R* and 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled precipitate is formed. Centrifuge and rinse the precipitate with three quantities, each of 2 mL, of *methanol R*. Carry out this operation rapidly and protected from bright light. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves easily.

TESTS

Appearance of solution. Dissolve 1.0 g in *methylene chloride R* and dilute to 10 mL with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Related substances. Examine by thin-layer chromatography (*2.2.27*), using a plate coated with a suitable octadecylsilyl silica gel (5 µm) with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution. Dissolve 1.0 g in a mixture of 1 volume of *methanol R* and 2 volumes of *methylene chloride R* and dilute to 20 mL with the same mixture of solvents.

Reference solution (a). Dilute 0.5 mL of the test solution to 100 mL with a mixture of 1 volume of *methanol R* and 2 volumes of *methylene chloride R*.

Reference solution (b). Dissolve 0.50 g of the substance to be examined in 25 mL of a 15 g/L solution of *potassium hydroxide R* in *methanol R* and add 1 mL of *water R*. Heat on a water-bath under a reflux condenser for 4 h. Cool and add 25 mL of *0.5 M hydrochloric acid*. Shake with 100 mL of *methylene chloride R*. Evaporate the lower layer to dryness on a water-bath. Dissolve the residue in 10 mL of a mixture of 1 volume of *methanol R* and 2 volumes of *methylene chloride R*, add 10 mL of the test solution and dilute to 25 mL with a mixture of 1 volume of *methanol R* and 2 volumes of *methylene chloride R*.

Apply separately to a plate (100 mm square) 1 µL of each solution. Develop in an unsaturated tank over a path of 7 cm using a mixture of 10 volumes of *methanol R*, 30 volumes of a 59 g/L solution of *sodium chloride R* and 60 volumes of *dioxan R*. Allow the plate to dry in an oven at 160 °C for 15 min and place the hot plate in a closed tank containing about 20 mL of *fuming nitric acid R* for 30 min. Remove the plate and heat it again at 160 °C for 15 min. Allow to cool and examine immediately in ultraviolet light at 254 nm. 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 (a) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated principal spots.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 40 mL of *alcohol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the two points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 48.91 mg of $C_{30}H_{33}ClN_2O_2$.

STORAGE

Store protected from light.

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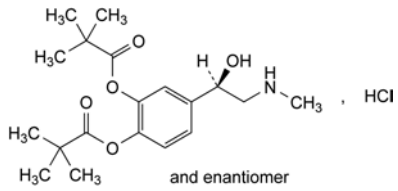
corrected 7.0

DIPIVEFRINE HYDROCHLORIDE

Dipivefrini hydrochloridum



$C_{19}H_{30}ClNO_5$ M_r 387.9
[64019-93-8]

DEFINITION

Hydrochloride of 4-[(1*RS*)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate).

Content: 97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, very soluble in methanol, freely soluble in ethanol (96 per cent) and in methylene chloride.

mp: about 160 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: discs.
Comparison: *dipivefrine hydrochloride CRS*.

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

TESTS

Impurities A and B. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 10.0 mL with the same acid.