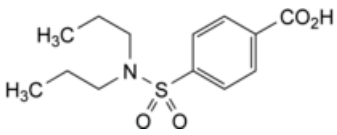
Edition: BP 2025 (Ph. Eur. 11.6 update)

Probenecid

General Notices

(Ph. Eur. monograph 0243)



$C_{13}H_{19}NO_4S$ 285.4 *57-66-9*

Action and use

Uricosuric drug.

Preparation

Probenecid Tablets

Ph Eur

DEFINITION

4-(Dipropylsulfamoyl)benzoic acid.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder or small crystals.

Solubility

Practically insoluble in water, soluble in acetone, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (2.2.14): 197 °C to 202 °C.
B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20 mg in a mixture of 1 volume of *0.1 M hydrochloric acid* and 9 volumes of *ethanol (96 per cent) R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 100.0 mL with a mixture of 1 volume of *0.1 M hydrochloric acid* and 9 volumes of *ethanol (96 per cent) R*.

Spectral range 220-350 nm.

Absorption maxima At 223 nm and 248 nm.

Specific absorbance at the absorption maximum at 248 nm 310 to 350.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *probenecid CRS*.

D. Dissolve 0.2 g in the smallest necessary quantity of *dilute ammonia R2* (about 0.6 mL). Add 3 mL of *silver nitrate solution R2*. A white precipitate is formed which dissolves in an excess of ammonia.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 1.0 g in *1 M sodium hydroxide* and dilute to 10 mL with the same solvent.

Acidity

To 2.0 g add 100 mL of *water R* and heat on a water-bath for 30 min. Make up to the original volume with *water R*, allow to cool to room temperature and filter. To 50 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. Not more than 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Solution A Mix 1 volume of *glacial acetic acid R* and 100 volumes of *acetonitrile R*.

Solution B Mix 1 volume of *glacial acetic acid R* and 100 volumes of a 6.9 g/L solution of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R* and adjust to pH 3.0 with *dilute phosphoric acid R*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *potassium 4-sulfobenzoate R* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Solution A, solution B (50:50 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 4 times the retention time of probenecid.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to probenecid (retention time = about 7 min): impurity A = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and probenecid.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.4;

— for each impurity, use the concentration of probenecid in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 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

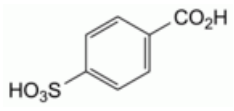
Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R*, shaking and heating slightly if necessary. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.54 mg of $C_{13}H_{19}NO_4S$.

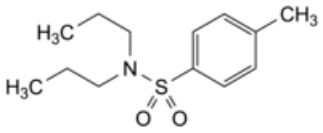
IMPURITIES

Specified impurities *A.*

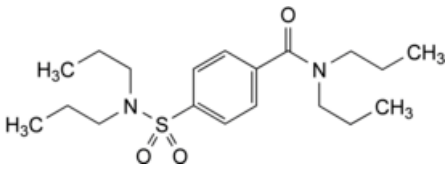
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



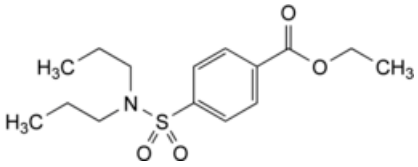
A. 4-sulfobenzoic acid,



B. 4-methyl-*N*,*N*-dipropylbenzenesulfonamide,



C. 4-(dipropylsulfamoyl)-*N*,*N*-dipropylbenzamide,



D. ethyl 4-(dipropylsulfamoyl)benzoate.

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