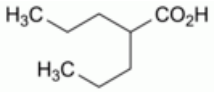
Edition: BP 2025 (Ph. Eur. 11.6 update)

# Valproic Acid

General Notices

*(Ph. Eur. monograph 1378)*



$C_8H_{16}O_2$ 144.2 *99-66-1*

**Action and use**

Antiepileptic.

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## DEFINITION

2-Propylpentanoic acid.

**Content**

99.0 per cent to 101.0 per cent.

## CHARACTERS

**Appearance**

Colourless or very slightly yellow, clear liquid, slightly viscous.

**Solubility**

Very slightly soluble in water, miscible with ethanol (96 per cent) and with methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

## IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison* *valproic acid CRS*.

## TESTS

**Appearance of solution**

The solution is clear (2.2.1) and not more intensely coloured than reference solution $Y_5$ (2.2.2, *Method II*).

Dissolve 2.0 g in *dilute sodium hydroxide solution R* and dilute to 10 mL with the same alkaline solution.

**Related substances**

Gas chromatography (2.2.28).

*Test solution* Dissolve 0.500 g of the substance to be examined in *heptane R* and dilute to 100.0 mL with the same solvent.

*Reference solution (a)* Dissolve 5 mg of *valproic acid for system suitability CRS* (containing impurity K) in 1.0 mL of *heptane R*.

*Reference solution (b)* Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*.

*Column*:

— *material*: wide-bore fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *macrogol 20 000 2-nitroterephthalate R* (film thickness 0.5 µm).

*Carrier gas* *helium for chromatography R*.

*Flow rate* 8 mL/min.

*Temperature*:

| | Time (min) | Temperature (°C) |
|---|---|---|
| Column | 0 - 5 | 80 |
| | 5 - 15 | 80 → 150 |
| | 15 - 28.3 | 150 → 190 |
| | 28.3 - 30 | 190 |
| Injection port | | 220 |
| Detector | | 220 |

*Detection* Flame ionisation.

*Injection* 1 µL.

*Relative retention* With reference to valproic acid (retention time = about 17 min): impurity K = about 0.97.

*System suitability* Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity K and valproic acid.

*Limits*:

— *impurity K*: not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.03 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

**Sulfated ash** (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

## ASSAY

Dissolve 0.100 g in 25 mL of *ethanol (96 per cent) R*. Add 2 mL of *water R*. 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 14.42 mg of $C_8H_{16}O_2$.

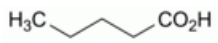
## STORAGE

In an airtight container.

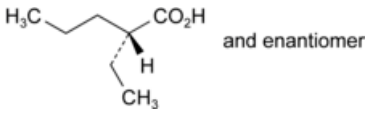
## IMPURITIES

*Specified impurities* *K*.

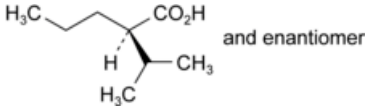
*Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



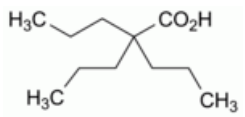

A. pentanoic acid (valeric acid),



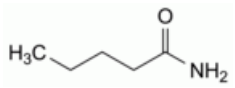

B. (2*RS*)-2-ethylpentanoic acid,



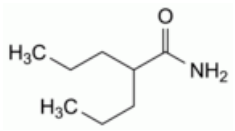

C. (2*RS*)-2-(1-methylethyl)pentanoic acid,



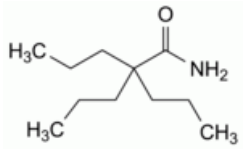

D. 2,2-dipropylpentanoic acid,



E. pentanamide (valeramide),

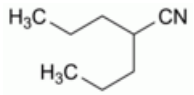


F. 2-propylpentanamide,

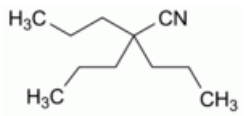


G. 2,2-dipropylpentanamide,

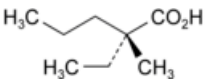
H. pentanenitrile (valeronitrile),



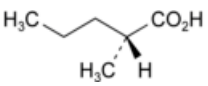
I. 2-propylpentanenitrile,



J. 2,2-dipropylpentanenitrile,

 and enantiomer

K. (2*RS*)-2-ethyl-2-methylpentanoic acid,

 and enantiomer

L. (2*RS*)-2-methylpentanoic acid.

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