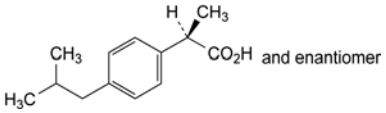
04/2008:0721
corrected 7.0

IBUPROFEN

Ibuprofenum



$C_{13}H_{18}O_2$ M_r 206.3
[15687-27-1]

DEFINITION

(2*RS*)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 75 °C to 78 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in a 4 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with the same alkaline solution.

Spectral range: 240-300 nm, using a spectrophotometer with a band width of 1.0 nm and a scan speed of not more than 50 nm/min.

Absorption maxima: at 264 nm and 272 nm.

Shoulder: at 258 nm.

Absorbance ratio:

- A_{264} / A_{258} = 1.20 to 1.30;
- A_{272} / A_{258} = 1.00 to 1.10.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ibuprofen CRS*.

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

Test solution. Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 50 mg of *ibuprofen CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel plate R.*

Mobile phase: *anhydrous acetic acid R, ethyl acetate R, hexane R* (5:24:71 *V/V/V*).

Application: 5 µL.

Development: over a path of 10 cm.

Drying: at 120 °C for 30 min.

Detection: lightly spray with a 10 g/L solution of *potassium permanganate R* in *dilute sulfuric acid R* and heat at 120 °C for 20 min; examine in ultraviolet light at 365 nm.

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

TESTS

Solution S. Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

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

Optical rotation (*2.2.7*): – 0.05° to + 0.05°.

Dissolve 0.50 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in 2 mL of *acetonitrile R1* and dilute to 10.0 mL with mobile phase A.

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

Reference solution (b). Dilute 1.0 mL of *ibuprofen impurity B CRS* to 10.0 mL with *acetonitrile R1* (solution A). Dissolve 20 mg of *ibuprofen CRS* in 2 mL of *acetonitrile R1*, add 1.0 mL of solution A and dilute to 10.0 mL with mobile phase A.

Reference solution (c). Dissolve the contents of a vial of *ibuprofen for peak identification CRS* (mixture of impurities A, J and N) in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

- *mobile phase A*: mix 0.5 volumes of *phosphoric acid R*, 340 volumes of *acetonitrile R1* and 600 volumes of *water R*; allow to equilibrate and dilute to 1000 volumes with *water R*;
- *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 15	0 → 85
55 - 70	15	85

Flow rate: 2 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *ibuprofen for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, J and N.

Relative retention with reference to ibuprofen (retention time = about 21 min): impurity J = about 0.2; impurity N = about 0.3; impurity A = about 0.9; impurity B = about 1.1.

System suitability: reference solution (b):

- *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity B, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen. If necessary, adjust the concentration of acetonitrile in mobile phase A.

Limits:

- *impurities A, J, N*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Impurity F. Gas chromatography (*2.2.28*): use the normalisation procedure.

Methylating solution. Dilute 1 mL of *N,N-dimethylformamide dimethylacetal R* and 1 mL of *pyridine R* to 10 mL with *ethyl acetate R*.

Test solution. Weigh about 50.0 mg of the substance to be examined into a sealable vial, dissolve in 1.0 mL of *ethyl acetate R*, add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Reference solution (a). Dissolve 0.5 mg of *ibuprofen impurity F CRS* in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Weigh about 50.0 mg of *ibuprofen CRS* into a sealable vial, dissolve in 1.0 mL of reference solution (a), add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Column:

– *material*: fused silica;
– *size*: *l* = 25 m, Ø = 0.53 mm;
– *stationary phase*: *macrogol 20 000 R* (film thickness 2 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 5.0 mL/min.

Temperature:

– *column*: 150 °C;
– *injection port*: 200 °C;
– *detector*: 250 °C.

Detection: flame ionisation.

Injection: 1 µL of the test solution and reference solution (b).

Run time: twice the retention time of ibuprofen.

System suitability:

– *relative retention* with reference to ibuprofen (retention time = about 17 min): impurity F = about 1.5.

Limit:

– *impurity F*: maximum 0.1 per cent.

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

12 mL of solution S complies with test B. Prepare the reference solution using lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with *methanol R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

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

ASSAY

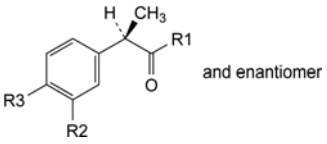
Dissolve 0.450 g in 50 mL of *methanol R*. Add 0.4 mL of *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a red colour is obtained. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

IMPURITIES

Specified impurities: A, F, J, N.

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, E, G, H, I, K, L, M, O, P, Q, R.*

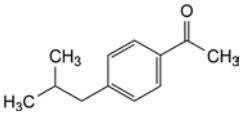


A. R1 = OH, R2 = CH_2-$CH(CH_3)_2$, R3 = H: (2*RS*)-2-[3-(2-methylpropyl)phenyl]propanoic acid,

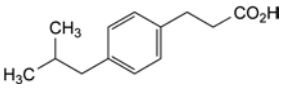
B. R1 = OH, R2 = H, R3 = $[CH_2]_3$-CH_3: (2*RS*)-2-(4-butylphenyl)propanoic acid,

C. R1 = NH_2, R2 = H, R3 = CH_2-$CH(CH_3)_2$: (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanamide,

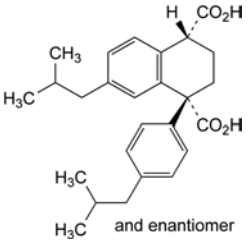
D. R1 = OH, R2 = H, R3 = CH_3: (2*RS*)-2-(4-methylphenyl)-propanoic acid,



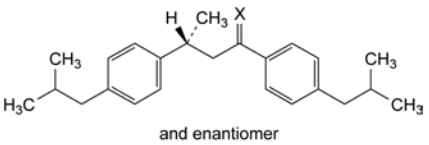
E. 1-[4-(2-methylpropyl)phenyl]ethanone,



F. 3-[4-(2-methylpropyl)phenyl]propanoic acid,

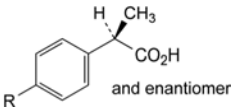


G. (1*RS*,4*RS*)-7-(2-methylpropyl)-1-[4-(2-methylpropyl)-phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid,



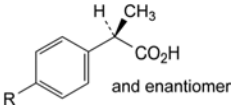
H. X = O: (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butan-1-one,

I. X = H_2: 1-(2-methylpropyl)-4-[(3*RS*)-3-[4-(2-methylpropyl)-phenyl]butyl]benzene,



J. R = CO-$CH(CH_3)_2$: (2*RS*)-2-[4-(2-methylpropanoyl)-phenyl]propanoic acid,

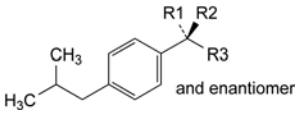
N. R = C_2H_5: (2*RS*)-2-(4-ethylphenyl)propanoic acid,



K. R = CHO: (2*RS*)-2-(4-formylphenyl)propanoic acid,

L. R = CHOH-$CH(CH_3)_2$: 2-[4-(1-hydroxy-2-methylpropyl)-phenyl]propanoic acid,

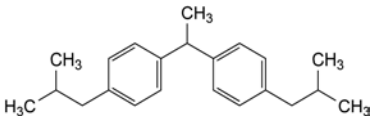
O. R = $CH(CH_3)$-C_2H_5: 2-[4-(1-methylpropyl)phenyl]propanoic acid,



M. R1 = OH, R2 = CH_3, R3 = CO_2H: (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid,

P. R1 = H, R2 = CH_3, R3 = CH_2OH: (2*RS*)-2-[4-(2-methylpropyl)-phenyl]propan-1-ol,

Q. R1 = R2 = H, R3 = CH_2OH: 2-[4-(2-methylpropyl)-phenyl]ethanol,



R. 1,1′-(ethane-1,1-diyl)-4,4′-(2-methylpropyl)dibenzene.

01/2008:0917
corrected 6.3

ICHTHAMMOL

Ichthammolum

DEFINITION

Ichthammol is obtained by distillation from certain bituminous schists, sulfonation of the distillate and neutralisation of the product with ammonia.

Content:

– *dry matter*: 50.0 per cent *m/m* to 56.0 per cent *m/m*;
– *total ammonia* (NH_3; M_r 17.03): 4.5 per cent *m/m* to 7.0 per cent *m/m* (dried substance);
– *organically combined sulfur*: minimum 10.5 per cent *m/m* (dried substance);
– *sulfur in the form of sulfate*: maximum 20.0 per cent *m/m* of the total sulfur.

CHARACTERS

Appearance: dense, blackish-brown liquid.

Solubility: miscible with water and with glycerol, slightly soluble in ethanol (96 per cent), in fatty oils and in liquid paraffin. It forms homogeneous mixtures with wool fat and soft paraffin.

IDENTIFICATION

A. Dissolve 1.5 g in 15 mL of *water R* (solution A). To 2 mL of solution A add 2 mL of *hydrochloric acid R*. A resinous precipitate is formed. Decant the supernatant liquid. The precipitate is partly soluble in *ether R*.

B. 2 mL of solution A, obtained in identification test A, gives the reaction of ammonium salts and salts of volatile bases (*2.3.1*).

C. Evaporate and ignite the mixture of solution A and *dilute sodium hydroxide solution R* obtained in identification test B. Take up the residue with 5 mL of *dilute hydrochloric acid R*. Gas is evolved which turns *lead acetate paper R* brown or black. Filter the solution. The filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

Acidity or alkalinity. To 10.0 mL of the clear filtrate obtained in the assay of total ammonia add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Relative density (*2.2.5*): 1.040 to 1.085, determined on a mixture of equal volumes of the substance to be examined and *water R*.

Sulfated ash (*2.4.14*): maximum 0.3 per cent, determined on 1.00 g.

ASSAY

Dry matter. Weigh 1.000 g in a tared flask containing 2 g of *sand R*, previously dried to constant mass, and a small glass rod. Heat on a water-bath for 2 h with frequent stirring and dry in an oven at 100-105 °C until 2 consecutive weighings do not differ by more than 2.0 mg; the 2nd weighing is carried out after drying again for 1 h.

Total ammonia. Dissolve 2.50 g in 25 mL of warm *water R*. Rinse the solution into a 250 mL volumetric flask, add 200 mL of *sodium chloride solution R* and dilute to 250.0 mL with *water R*. Filter the solution, discarding the first 20 mL of filtrate. To 100.0 mL of the clear filtrate add 25 mL of *formaldehyde solution R*, neutralised to *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 1.703 mg of NH_3.

Organically combined sulfur. Mix 0.500 g with 4 g of *anhydrous sodium carbonate R* and 3 mL of *methylene chloride R* in a porcelain crucible of about 50 mL capacity, warm and stir until all the methylene chloride has evaporated. Add 10 g of coarsely powdered *copper nitrate R*, mix thoroughly and heat the mixture very gently using a small flame. When the initial reaction has subsided, increase the temperature slightly until most of the material has blackened. Cool, place the crucible in a large beaker, add 20 mL of *hydrochloric acid R* and, when the reaction has ceased, add 100 mL of *water R* and boil until all the copper oxide has dissolved. Filter the solution, add 400 mL of *water R*, heat to boiling and add 20 mL of *barium chloride solution R1*. Allow to stand for 2 h, filter, wash with *water R*, dry and ignite at about 600 ± 50 °C until 2 successive weighings do not differ by more than 0.2 per cent of the mass of the residue.

1 g of residue is equivalent to 0.1374 g of total sulfur.

Calculate the percentage content of total sulfur and subtract the percentage content of sulfur in the form of sulfate.

Sulfur in the form of sulfate. Dissolve 2.000 g in 100 mL of *water R*, add 2 g of *cupric chloride R* dissolved in 80 mL of *water R* and dilute to 200.0 mL with *water R*. Shake and filter. Heat 100.0 mL of the filtrate almost to boiling, add 1 mL of *hydrochloric acid R* and 5 mL of *barium chloride solution R1* dropwise and heat on a water-bath. Filter, wash the precipitate with *water R*, dry and ignite at about 600 ± 50 °C until 2 successive weighings do not differ by more than 0.2 per cent of the mass of the residue.

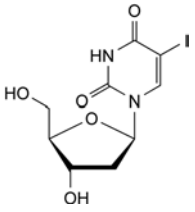
1 g of residue is equivalent to 0.1374 g of sulfur present in the form of sulfate.

Calculate the percentage content of sulfur in the form of sulfate.

01/2008:0669

IDOXURIDINE

Idoxuridinum



$C_9H_{11}IN_2O_5$ M_r 354.1
[54-42-2]