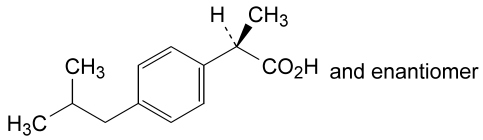
01/2008:0721
corrected 6.0

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. 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. Examined between 240 nm and 300 nm (*2.2.25*), using a spectrophotometer with a band width of 1.0 nm and a scan speed of not more than 50 nm/min, the solution shows a shoulder at 258 nm and 2 absorption maxima, at 264 nm and 272 nm. The ratio of the absorbance measured at the maximum at 264 nm to that measured at the shoulder at 258 nm is 1.20 to 1.30. The ratio of the absorbance measured at the maximum at 272 nm to that measured at the shoulder at 258 nm is 1.00 to 1.10.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

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 sulphuric 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*).

Angle of 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 R* 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.

Reference solution (b). Dissolve 20 mg of *ibuprofen CRS* in 2 ml of *acetonitrile R*, add 1.0 ml of a 0.06 g/l solution of *ibuprofen impurity B CRS* in *acetonitrile R* and dilute to 10.0 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 R* and 600 volumes of *water R*; allow to equilibrate and dilute to 1000 volumes with *water R*,
– *mobile phase B*: *acetonitrile R*,

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
70 - 75	15 → 100	85 → 0

Flow rate: 2 ml/min.

Detection: spectrophotometer at 214 nm.

Equilibration: for about 45 min with mobile phase A.

Injection: 20 µl.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum of 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:

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
– *any other impurity*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),
– *total of all impurities apart from impurity B*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent),

– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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

Methylating solution. Dilute 1 ml of *N,N-dimethylformamide dimethyl acetal 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 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 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; inject 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 limit test B. Prepare the standard using lead standard solution (1 ppm Pb) prepared 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* over *diphosphorus pentoxide R*.

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

ASSAY

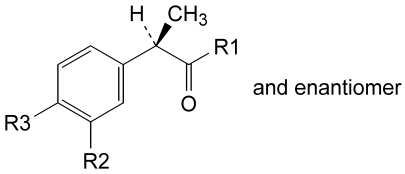
Dissolve 0.450 g in 50 ml of *methanol R*. Add 0.4 ml of *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a red colour is obtained. Carry out a blank titration.

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, B, C, D, E.

Other detectable impurities: F, G, H, I, J, K, L, M, N, O, P, Q, R.

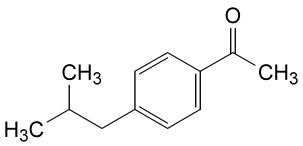


A. R1 = OH, R2 = CH_2-$CH(CH_3)_2$, R3 = H: (2*RS*)-2-[3-(2-methylpropyl)phenyl]propanoic acid,

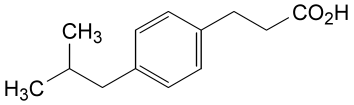
B. R1 = OH, R2 = H, R3 = $[CH_2]_3$-CH_3: (2*RS*)-2-(4-butylphenyl)propanoic acid,

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

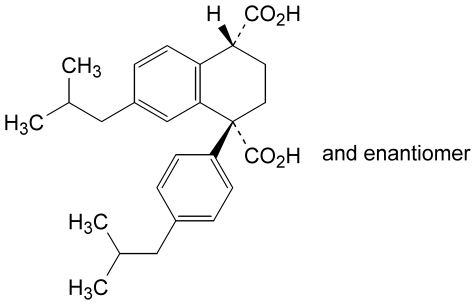
D. R1 = OH, R2 = H, R3 = CH_3: (2*RS*)-2-(4-methylphenyl)propanoic acid,



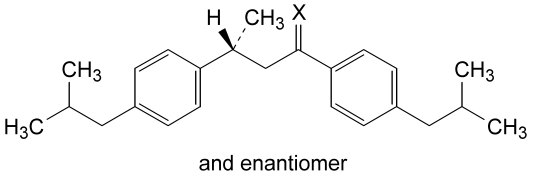
E. 1-[4-(2-methylpropyl)phenyl]ethanone,



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

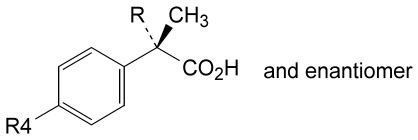


G. *cis*-7-(2-methylpropyl)-1-[4-(2-methylpropyl)phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid,



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

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



J. R = H, R4 = CO-CH(CH_3)$_2$: (2*RS*)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,

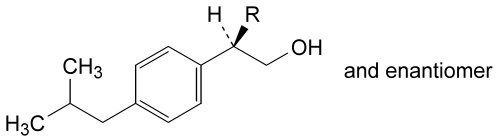
K. R = H, R4 = CHO: (2*RS*)-2-(4-formylphenyl)propanoic acid,

L. R = H, R4 = CHOH-CH(CH_3)$_2$: 2-[4-(1-hydroxy-2-methylpropyl)phenyl]propanoic acid,

M. R = OH, R4 = CH_2-CH(CH_3)$_2$: (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid,

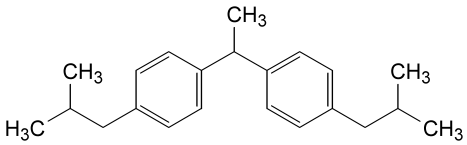
N. R = H, R4 = C_2H_5: (2*RS*)-2-(4-ethylphenyl)propanoic acid,

O. R = H, R4 = CH(CH_3)-C_2H_5: 2-[4-(1-methylpropyl)phenyl]propanoic acid,



P. R = CH_3: (2*RS*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol,

Q. R = H: 2-[4-(2-methylpropyl)phenyl]ethanol,



R. 1,1-bis[4-(2-methylpropyl)phenyl]ethane.

01/2008:1439
corrected 6.0

ICELAND MOSS

Lichen islandicus

DEFINITION

Whole or cut, dried thallus of *Cetraria islandica* (L.) Acharius s.l.

IDENTIFICATION

A. The thallus, up to 15 cm long, is irregularly dichotomous and consists of glabrous, groove-shaped or almost flat, stiff, brittle bands, 0.3-1.5 cm wide and about 0.5 mm thick, sometimes serrated with the margin appearing ciliated (pycnidia). The upper surface is greenish or greenish-brown, the lower surface is greyish-white or light brownish and shows whitish, depressed spots (so-called respiratory cavities). On the apices of the terminal lobes, very rarely, there are brown, discoid apothecia.

B. Reduce to a powder (355) (*2.9.12*). The powder is greyish-brown. Examine under a microscope, using *chloral hydrate solution R*. The powder shows the following diagnostic characters: numerous fragments of the pseudoparenchyma consisting of narrow-lumened, thick-walled hyphae from the marginal layer and wide-lumened hyphae from the adjacent layer consisting of loosely entwined hyphae, in which, in the medullary zone, greenish or brownish algae cells up to 15 µm in diameter, are embedded; occasionally marginal fragments of the thallus with tube-like or cylindrical spermogonia, up to about 160 µm wide and up to about 400 µm long.

C. To 1.0 g of the powdered drug (355) (*2.9.12*) add 10 ml of *water R* and boil for 2-3 min. The greyish-brown solution forms a gel after cooling which gives a blue colour with *iodine solution R*.

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

Test solution. To 1.0 g of the powdered drug (355) (*2.9.12*) add 5 ml of *acetone R* and heat in a water-bath under a reflux condenser for 2-3 min. Cool and filter.

Reference solution. Dissolve 5 mg of *anethole R* and 5 mg of *caffeic acid R* in 2 ml of *acetone R*.

Plate: *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

Mobile phase: *acetone R, methanol R, anhydrous formic acid R, toluene R* (5:5:10:80 *V/V/V/V*).

Application: 20 µl [or 4 µl] of the test solution and 10 µl [or 2 µl] of the reference solution, as bands.

Development: over a path of 10 cm [or 6 cm].

Drying: in air.

Detection: spray with *anisaldehyde solution R*. Heat at 100-105 °C for 5-10 min and examine in daylight.

Results: see below the sequence of zones present in the chromatograms obtained with the reference solution and the test solution. Furthermore, other faint zones may be present in the chromatogram obtained with the test solution.

Top of the plate	
	A greyish-blue zone
Anethole: a blue or bluish-violet zone	
———	———
	2 weak greyish-blue zones
	A weak greyish-brown or grey zone
———	———
	A greyish-violet zone
Caffeic acid: a greyish-blue zone	
Reference solution	**Test solution**

TESTS

Foreign matter (*2.8.2*): maximum 5 per cent.

Loss on drying (*2.2.32*): maximum 12.0 per cent, determined on 1.000 g of powdered drug (355) (*2.9.12*) by drying in an oven at 105 °C for 2 h.

Total ash (*2.4.16*): maximum 3.0 per cent.

Swelling value (*2.8.4*): minimum 4.5, determined on the powdered drug (355) (*2.9.12*).

ERRATA

In the following monographs, after the heading ‘Other detectable impurities’ in the Impurities section, read:

‘(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*)’

Articaine hydrochloride (1688)
Biperiden hydrochloride (1074)
Caffeine (0267)
Caffeine monohydrate (0268)
Ibuprofen (0721)
Ifosfamide (1529)
Metformin hydrochloride (0931)
Naphazoline hydrochloride (0730)
Norethisterone acetate (0850)
Oxaliplatin (2017)
Potassium clavulanate (1140)
Potassium clavulanate, diluted (1653)
Testosterone propionate (0297)
Thiamine hydrochloride (0303)
Thiamine nitrate (0531)
Tranexamic acid (0875)