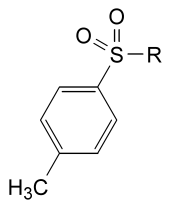

E. [(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulphonate.

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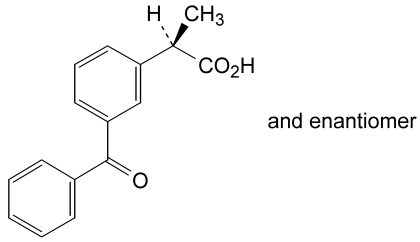
KETOPROFEN

Ketoprofenum



$C_{16}H_{14}O_3$ M_r 254.3
[22071-15-4]

DEFINITION

(2*RS*)-2-(3-Benzoylphenyl)propanoic acid.

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 94 °C to 97 °C.

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

Test solution. Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with *ethanol (96 per cent) R*.

Spectral range: 230-350 nm.

Absorption maximum: at 255 nm.

Specific absorbance at the absorption maximum: 615 to 680.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ketoprofen CRS*.

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

Test solution. Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 10 mg of *ketoprofen CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *indometacin CRS* in *acetone R* and dilute to 10 ml with the same solvent. To 1 ml of this solution add 1 ml of reference solution (a).

Plate: *TLC silica gel GF_{254} plate R.*

Mobile phase: *glacial acetic acid R, methylene chloride R, acetone R* (1:49:50 *V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated principal spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in obtained with reference solution (a).

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 *acetone R* and dilute to 10 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *ketoprofen impurity A CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *ketoprofen impurity C CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (d). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. To 1.0 ml of this solution add 1.0 ml of reference solution (b).

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm.

Mobile phase: mix 2 volumes of freshly prepared *phosphate buffer solution pH 3.5 R*, 43 volumes of *acetonitrile R* and 55 volumes of *water R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 233 nm.

Injection: 20 µl.

Run time: 7 times the retention time of ketoprofen.

Relative retention with reference to ketoprofen (retention time = about 7 min): impurity C = about 0.34; impurity H = about 0.39; impurity G = about 0.46; impurity E = about 0.69; impurity B = about 0.73; impurity D = about 1.35; impurity I = about 1.43;

impurity A = about 1.50; impurity J = about 1.86;
impurity F = about 1.95; impurity K = about 2.27;
impurity L = about 2.49.

System suitability: reference solution (d):

– *resolution*: minimum 7.0 between the peaks due to ketoprofen and impurity A.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatograms obtained with reference solution (b) (0.2 per cent);

– *impurity C*: not more than the area of the principal peak in the chromatograms obtained with reference solution (c) (0.2 per cent);

– *impurities B, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatograms obtained with reference solution (a) (0.2 per cent);

– *sum of impurities other than A and C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Heavy metals (*2.4.8*: maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g at 60 °C at a pressure not exceeding 670 Pa.

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

ASSAY

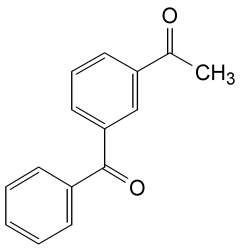
Dissolve 0.200 g in 25 ml of *ethanol (96 per cent) R*. Add 25 ml of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M sodium hydroxide* is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

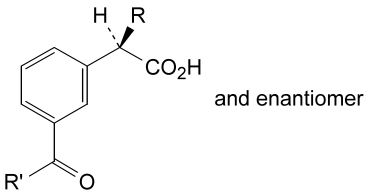
IMPURITIES

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

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*): *G, H, I, J, K, L.*

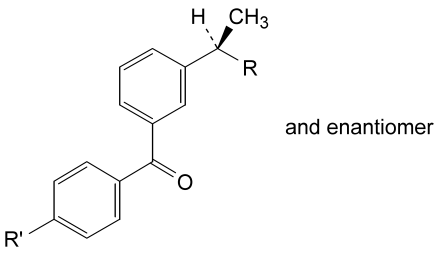


A. 1-(3-benzoylphenyl)ethanone,



B. R = H, R′ = C_6H_5: (3-benzoylphenyl)acetic acid,

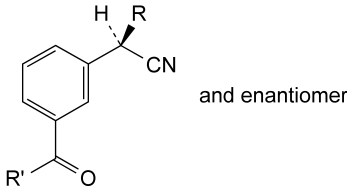
C. R = CH_3, R′ = OH: 3-[(1*RS*)-1-carboxyethyl]benzoic acid,



D. R = CO_2H, R′ = CH_3: (2*RS*)-2-[3-(4-methylbenzoyl)phenyl]-propanoic acid,

E. R = CO-NH_2, R′ = H: (2*RS*)-2-(3-benzoylphenyl)propanamide,

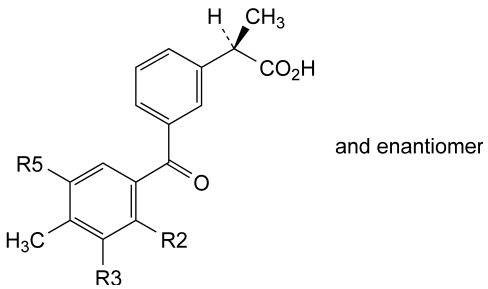
F. R = CN, R′ = H: (2*RS*)-2-(3-benzoylphenyl)propanenitrile,



G. R = CH_3, R′ = OH: 3-[(1*RS*)-1-cyanoethyl]benzoic acid,

H. R = H, R′ = OH: 3-(cyanomethyl)benzoic acid,

I. R = H, R′ = C_6H_5: (3-benzoylphenyl)ethanenitrile,



J. R2 = CH_3, R3 = R5 = H: (2*RS*)-2-[3-(2,4-dimethylbenzoyl)phenyl]propanoic acid,

K. R2 = R3 = CH_3, R5 = H + R2 = H, R3 = R5 = CH_3: mixture of (2*RS*)-2-[3-(2,3,4-trimethylbenzoyl)phenyl]propanoic acid and (2*RS*)-2-[3-(3,4,5-trimethylbenzoyl)phenyl]propanoic acid,

L. R2 = R5 = CH_3, R3 = H: (2*RS*)-2-[3-(2,4,5-trimethylbenzoyl)phenyl]propanoic acid.