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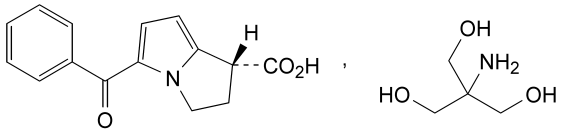
KETOROLAC TROMETAMOL

Ketorolacum trometamolum



and enantiomer

$C_{19}H_{24}N_2O_6$ M_r 376.4
[74103-07-4]

DEFINITION

2-Amino-2-(hydroxymethyl)propane-1,3-diol (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ketorolac trometamol CRS*.

TESTS

Solution S. Dissolve 0.75 g in *carbon dioxide-free water R* and dilute to 25.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*).

pH (*2.2.3*): 5.7 to 6.7.

Dilute 5 ml of solution S to 15 ml with *carbon dioxide-free water R*.

Absorbance (*2.2.25*): maximum 0.10, determined at 430 nm for solution S.

Related substances. Liquid chromatography (*2.2.29*). *Protect the solutions from bright light.*

Solvent mixture: *tetrahydrofuran R, water R* (30:70 *V/V*).

Test solution. Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 50 ml with the solvent mixture.

Reference solution (a). Dilute 1.0 ml of the test solution to 10.0 ml with the solvent mixture. Dilute 1.0 ml of this solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 2 mg of *ketorolac trometamol for peak identification CRS* (containing impurities A, B, C and D) in 5 ml of the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 40 °C.

Mobile phase: mix 30 volumes of *tetrahydrofuran R* with 70 volumes of a solution prepared as follows: dissolve 5.75 g of *ammonium dihydrogen phosphate R* in 900 ml of *water R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 ml with *water R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 313 nm.

Injection: 10 µl.

Run time: 3 times the retention time of ketorolac.

Identification of impurities: use the chromatogram supplied with *ketorolac trometamol for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention with reference to ketorolac (retention time = about 10 min): impurity C = about 0.5; impurity A = about 0.6; impurity D = about 0.7; impurity B = about 0.9.

System suitability: reference solution (b):

- *resolution*: minimum 1.5 between the peaks due to impurity B and ketorolac.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.67; impurity B = 0.52; impurity C = 2.2;
- *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test F. 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 by drying *in vacuo* at 60 °C for 3 h.

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

ASSAY

Dissolve 0.300 g in 60 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 37.64 mg of $C_{19}H_{24}N_2O_6$.

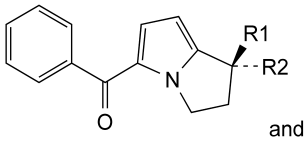
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D.

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*): *E, F, G, H, I, J.*



and enantiomer

A. R1 = H, R2 = OH: (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizin-1-ol,

B. R1 + R2 = O: 5-benzoyl-2,3-dihydro-1*H*-pyrrolizin-1-one,

D. R1 = CO_2H, R2 = OCH_3: (1*RS*)-5-benzoyl-1-methoxy-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,

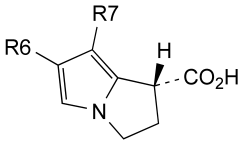
E. R1 = H, R2 = CO-NH-$C(CH_2OH)_3$: (1*RS*)-5-benzoyl-*N*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-2,3-dihydro-1*H*-pyrrolizine-1-carboxamide,

G. R1 = CO_2CH_3, R2 = OH: methyl (1*RS*)-5-benzoyl-1-hydroxy-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate,

H. R1 = H, R2 = CO_2CH_3: methyl (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate,

I. R1 = R2 = H: phenyl(2,3-dihydro-1*H*-pyrrolizin-5-yl)methanone,

J. R1 = H, R2 = $CO_2C_2H_5$: ethyl (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate,



and enantiomer

C. R6 = CO-C_6H_5, R7 = H: (1*RS*)-6-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,

F. R6 = H, R7 = CO-C_6H_5: (1*RS*)-7-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid.

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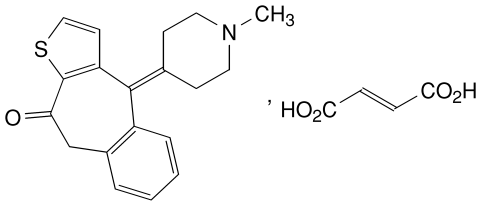
corrected 6.0

KETOTIFEN HYDROGEN FUMARATE

Ketotifeni hydrogenofumaras



$C_{23}H_{23}NO_5S$ M_r 425.5
[34580-14-8]

DEFINITION

4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.

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

CHARACTERS

Appearance: white to brownish-yellow, fine, crystalline powder.

Solubility: sparingly soluble in water, slightly soluble in methanol, very slightly soluble in acetonitrile.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of ketotifen hydrogen fumarate.*

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

Test solution. Dissolve 40 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 11 mg of *fumaric acid CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Plate: *cellulose for chromatography F_{254} R* as the coating substance.

Mobile phase: *water R, anhydrous formic acid R, di-isopropyl ether R* (3:7:90 *V/V/V*).

Application: 5 µl.

Development: over a path of 17 cm.

Drying: in a current of warm air.

Detection: examine in ultraviolet light at 254 nm. Spray lightly with a 5 g/l solution of *potassium permanganate R* in a 1.4 per cent *V/V* solution of *sulphuric acid R*. Examine in daylight by transparency.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_4, BY_4 or B_4 (*2.2.2, Method II*).

Dissolve 0.2 g in *methanol R* and dilute to 10 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 30.0 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 100.0 ml with the same mixture of solvents.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with a mixture of equal volumes of *methanol R* and *water R*. Dilute 1.0 ml to 10.0 ml with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (b). Dissolve 3.0 mg of *ketotifen impurity G CRS* in 10 ml of *methanol R* and dilute to 20.0 ml with *water R. Protect the solution from light.*

Reference solution (c). To 1.5 ml of reference solution (b) add 1.0 ml of the test solution and dilute to 10.0 ml with a mixture of equal volumes of *methanol R* and *water R. Protect the solution from light.*

Reference solution (d). Dilute 0.5 ml of reference solution (b) to 50.0 ml with a mixture of equal volumes of *methanol R* and *water R. Protect the solution from light.*

Column:

– *size*: *l* = 0.15 m, Ø = 4.0 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm),

– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: mix 175 µl of *triethylamine R* and 500 ml of *water R*,