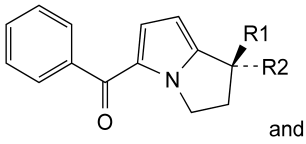


and enantiomer

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,

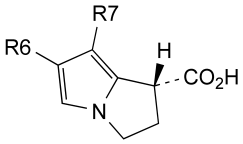
E. R1 = H, R2 = CO-NH-$C(CH_2OH)_3$: (1*RS*)-5-benzoyl-*N*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-2,3-dihydro-1*H*-pyrrolizine-1-carboxamide,

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

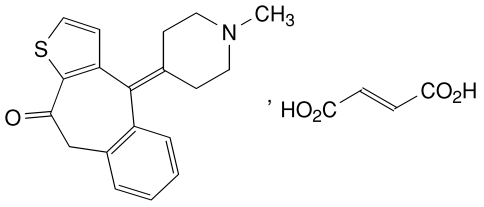
C. R6 = CO-C_6H_5, R7 = H: (1*RS*)-6-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,

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

01/2008:1592
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*,

– *mobile phase B*: mix 175 µl of *triethylamine R* and 500 ml of *methanol R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	40	60
12 - 20	40 → 10	60 → 90
20 - 25	10	90
25 - 26	10 → 40	90 → 60
26 - 31	40	60

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 297 nm.

Injection: 20 µl; inject the test solution and reference solutions (a), (c) and (d).

Relative retentions with reference to ketotifen: impurity D = about 0.31; impurity C = about 0.61; impurity G = about 0.86; impurity E = about 1.18; impurity F = about 1.36; impurity B = about 1.72; impurity A = about 2.15.

System suitability:

– *resolution*: minimum of 1.5 between the peaks due to ketotifen and to impurity G in the chromatogram obtained with reference solution (c),

– *signal-to-noise ratio*: minimum of 70 for the principal peak in the chromatogram obtained with reference solution (d).

Limits:

– *correction factor*: for the calculation of contents, multiply the area of the corresponding peak by the following correction factor: impurity G = 1.36,

– *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

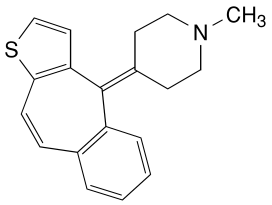
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

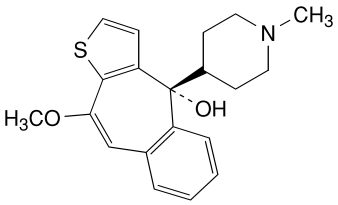
Dissolve 0.350 g in a mixture of 30 ml of *anhydrous acetic acid R* and 30 ml of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 42.55 mg of $C_{23}H_{23}NO_5S$.

IMPURITIES

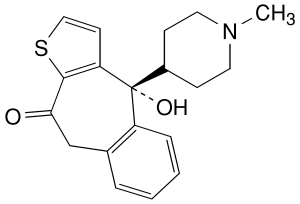


A. 4-(4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)-1-methylpiperidine,



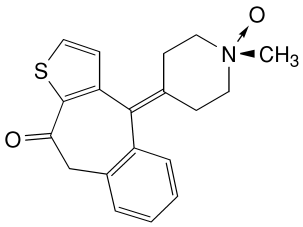
and enantiomer

B. (4*RS*)-10-methoxy-4-(1-methylpiperidin-4-yl)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ol,



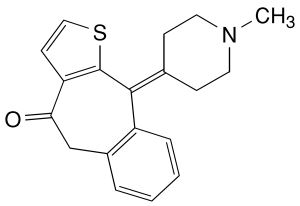
and enantiomer

C. (4*RS*)-4-hydroxy-4-(1-methylpiperidin-4-yl)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one,

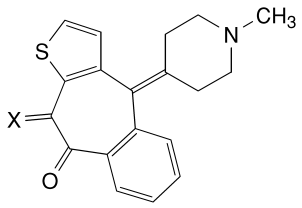


and enantiomer

D. 4-[(*aRaS*)-1-methylpiperidin-4-ylidene]-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one *N*-oxide (ketotifen *N*-oxide),



E. 10-(1-methylpiperidin-4-ylidene)-5,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophen-4-one,



F. X = H_2: 4-(1-methylpiperidin-4-ylidene)-4,10-dihydro-9*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-9-one,

G. X = O: 4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-9,10-dione.

01/2008:1885
corrected 6.0

KNOTGRASS

Polygoni avicularis herba

DEFINITION

Whole or cut dried flowering aerial parts of *Polygonum aviculare* L. *s.l.*

Content: minimum 0.30 per cent of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$; M_r 464.4) (dried drug).

IDENTIFICATION

A. The stem is 0.5 mm to 2 mm thick, branched, with nodes, cylindrical or slightly angular and longitudinally striated. It bears sessile or shortly petiolate, glabrous entire leaves, which differ widely in shape and size. The sheath-like stipules (ochrea) are lacerate and silvery. The small axillary flowers have 5 greenish-white perianth segments, the tips of which are often coloured red. The fruits are 2 mm to 4 mm, brown to black triangular nuts, usually punctate or striate.

B. Reduce to a powder (355) (*2.9.12*). The powder is greenish-brown. Examine under a microscope using *chloral hydrate solution R*. The powder shows the following diagnostic characters: fragments of the leaf epidermis with polygonal to sinuous cell walls and numerous anisocytic stomata (*2.8.3*), with a striated cuticle; fragments of leaves and stems containing numerous calcium oxalate clusters, some of them very large; groups of thick-walled fibres from the hypodermis of the stem; globular pollen grains with smooth exine and 3 germinal pores; occasional brown fragments of the exocarp composed of cells with thick sinuous walls. Examine under a microscope using a 675 g/l solution of *potassium hydroxide R*. Heat gently. The epidermis of the leaves and a few cells of the mesophyll stain red to reddish-violet. Examine under a microscope using a 0.1 g/l solution of *ferric chloride R*. Leaf fragments are stained almost black.

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

Test solution. To 1.0 g of the powdered drug (355) (*2.9.12*) add 10 ml of *methanol R*. Heat the mixture under a reflux condenser, in a water-bath for 10 min. Cool and filter.

Reference solution. Dissolve 1 mg of *caffeic acid R*, 2.5 mg of *hyperoside R* and 1 mg of *chlorogenic acid R* in 10 ml of *methanol R*.

Plate: *TLC silica gel plate R*.

Mobile phase: *anhydrous formic acid R, glacial acetic acid R, water R, ethyl acetate R* (7:7:14:72 *V/V/V/V*).

Application: 20 µl, as bands.

Development: over a path of 10 cm.

Drying: at 100-105 °C.

Detection: spray with a 10 g/l solution of *diphenylboric acid aminoethyl ester R* in *methanol R* subsequently spray with a 50 g/l solution of *macrogol 400 R* in *methanol R*. Allow the plate to dry in air for about 30 min. Examine in ultraviolet light at 365 nm.

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

Top of the plate	
Caffeic acid: a light blue fluorescent zone	1 or 2 blue fluorescent zones (caffeic acid)
———	———
	1 or 2 yellowish-green fluorescent zones
	A yellow fluorescent zone
Hyperoside: a yellowish-brown fluorescent zone	
	A yellowish-brown fluorescent zone
Chlorogenic acid: a light blue fluorescent zone	A light blue fluorescent zone (chlorogenic acid)
———	———
	A yellowish-brown fluorescent zone
Reference solution	**Test solution**

TESTS

Foreign matter (*2.8.2*): maximum 2 per cent of roots and maximum 2 per cent of other foreign matter.

Loss on drying (*2.2.32*): maximum 10.0 per cent, determined on 1.000 g of powdered drug (710) (*2.9.12*) by drying in an oven at 105 °C for 2 h.

Total ash (*2.4.16*): maximum 10.0 per cent.

ASSAY

Stock solution. In a 100 ml round-bottomed flask, place 0.800 g of the powdered drug (355) (*2.9.12*), add 1 ml of a 5 g/l solution of *hexamethylenetetramine R*, 20 ml of *acetone R* and 2 ml of *hydrochloric acid R1*. Boil the mixture under a reflux condenser for 30 min. Filter the liquid through a plug of absorbent cotton into a flask. Add the absorbent cotton to the residue in the round-bottomed flask and extract with 2 quantities, each of 20 ml, of *acetone R*, each time boiling under a reflux condenser for 10 min. Allow to cool, filter each extract through the plug of absorbent cotton into the flask. Filter the combined acetone extracts through a filter paper into a volumetric flask, dilute to 100.0 ml with *acetone R* rinsing the flask and the filter paper. Introduce 20.0 ml of the solution into a separating funnel, add 20 ml of *water R* and shake the mixture with 1 quantity of 15 ml and then 3 quantities, each of 10 ml of *ethyl acetate R*. Combine the ethyl acetate extracts in a separating funnel and wash with 2 quantities, each of 50 ml, of *water R*. Filter the extracts over 10 g of *anhydrous sodium sulphate R* into a 50 ml volume tric flask and dilute to volume with *ethyl acetate R*.