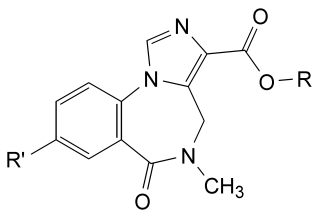
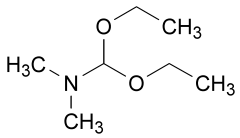


A. R = H, R′ = F: 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid,

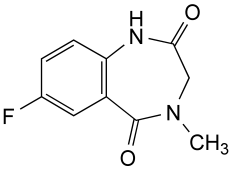
B. R = C_2-H_5, R′ = OH: ethyl 8-hydroxy-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,

E. R = C_2H_5, R′ = H: ethyl 5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,

F. R = C_2H_5, R′ = Cl: ethyl 8-chloro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,



C. diethoxy-*N*,*N*-dimethylmethanamine,

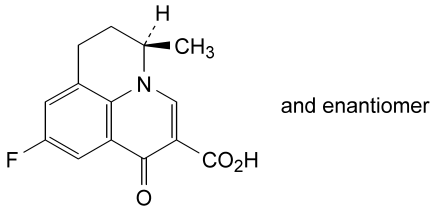


D. 7-fluoro-4-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione.

01/2008:1517
corrected 6.0

FLUMEQUINE

Flumequinum



$C_{14}H_{12}FNO_3$ M_r 261.3
[42835-25-6]

DEFINITION

(*RS*)-9-Fluoro-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]-quinolizine-2-carboxylic acid.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, microcrystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in methanol. It is freely soluble in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *flumequine CRS.*

B. Optical rotation (see Tests).

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

Test solution. Dissolve 5 mg of the substance to be examined in 10 ml of *methylene chloride R.*

Reference solution. Dissolve 5 mg of *flumequine CRS* in 10 ml of *methylene chloride R.*

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

Mobile phase: *ammonia R, water R, ethanol (96 per cent) R* (10:10:90 *V/V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

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

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 ml of *water R*, 0.05 ml of *phenolphthalein solution R1* and about 2 ml of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 ml of *alizarin S solution R* and 0.1 ml of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution changes from red to yellow and the blank remains red.

TESTS

Solution S. Dissolve 5.00 g in *0.5 M sodium hydroxide* and dilute to 50.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 35.0 mg of the substance to be examined in *dimethylformamide R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve the contents of a vial of *flumequine impurity B CRS* in 2.0 ml of a 50 µg/ml solution of *flumequine CRS* in *dimethylformamide R.*

Reference solution (b). Dilute 1.0 ml of the test solution to 200.0 ml with *dimethylformamide R.*

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *methanol R*, 1.36 g/l solution of *potassium dihydrogen phosphate R* (49:51 *V/V*).

Flow rate: 0.8 ml/min.

Detection: spectrophotometer at 313 nm.

Injection: 10 µl; inject *dimethylformamide R* as a blank.

Run time: 3 times the retention time of flumequine.

Relative retention with reference to flumequine (retention time = about 13 min): impurity A = about 0.67; impurity B = about 0.85.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity B and flumequine.

Limits:

– *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 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 by drying in an oven at 105 °C for 3 h.

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

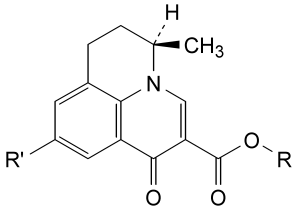
ASSAY

Dissolve 0.500 g in 50 ml of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 26.13 mg of $C_{14}H_{12}FNO_3$.

IMPURITIES

Specified impurities: A, B.



and enantiomer

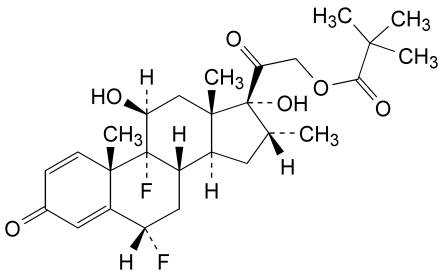
A. R = R′ = H: (*RS*)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic acid (defluoroflumequine),

B. R = C_2H_5, R′ = F: ethyl (*RS*)-9-fluoro-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylate (flumequine ethyl ester).

01/2008:1327
corrected 6.0

FLUMETASONE PIVALATE

Flumetasoni pivalas



$C_{27}H_{36}F_2O_6$ M_r 494.6
[2002-29-1]

DEFINITION

6α,9-Difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

Content: 97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *flumetasone pivalate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. 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 *flumetasone pivalate CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *desoxycortone acetate CRS* in *acetone R* and dilute to 10 ml with the same solvent. Dilute 5 ml of this solution to 10 ml with reference solution (a).

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

Mobile phase: add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

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

Detection B: spray with *alcoholic solution of sulphuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

C. Add about 2 mg to 2 ml of a mixture of 0.5 ml of *water R* and 1.5 ml of *sulphuric acid R* and shake to dissolve. Within 5 min, a pink colour develops. Add this solution to 10 ml of *water R* and mix. The colour fades and a clear solution remains.

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 ml of *water R*, 0.05 ml of *phenolphthalein solution R1* and about 1 ml of *dilute hydrochloric acid R* to render the