ASSAY

Dissolve 0.600 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 75 ml of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

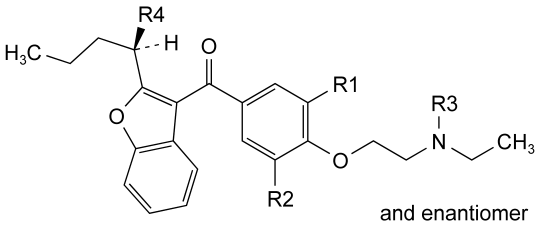
1 ml of *0.1 M sodium hydroxide* is equivalent to 68.18 mg of $C_{25}H_{30}ClI_2NO_3$.

STORAGE

Protected from light, at a temperature not exceeding 30 °C.

IMPURITIES

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

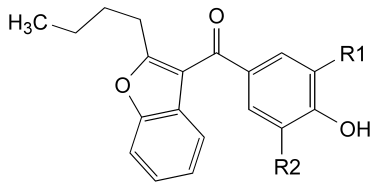


A. R1 = R2 = R4 = H, R3 = C_2H_5: (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]phenyl]methanone,

B. R1 = R2 = I, R3 = R4 = H: (2-butylbenzofuran-3-yl)[4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl]methanone,

C. R1 = I, R2 = R4 = H, R3 = C_2H_5: (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3-iodophenyl]methanone,

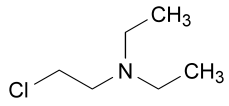
G. R1 = R2 = I, R3 = C_2H_5, R4 = OCH_3: [2-[(1*RS*)-1-methoxybutyl]benzofuran-3-yl][4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone,



D. R1 = R2 = I: (2-butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone,

E. R1 = R2 = H: (2-butylbenzofuran-3-yl)(4-hydroxyphenyl)methanone,

F. R1 = I, R2 = H: (2-butylbenzofuran-3-yl)(4-hydroxy-3-iodophenyl)methanone,

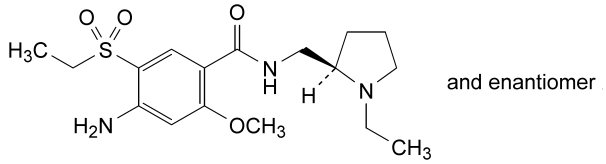


H. 2-chloro-*N*,*N*-diethylethanamine (2-chlorotriethylamine,(2-chloroethyl)diethylamine).

01/2008:1490
corrected 6.0

AMISULPRIDE

Amisulpridum



$C_{17}H_{27}N_3O_4S$ M_r 369.5
[71675-85-9]

DEFINITION

4-Amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

mp: about 126 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *amisulpride CRS*.

TESTS

Appearance of solution. The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 1.0 g in 3 ml of a mixture of 1 volume of *acetic acid R* and 4 volumes of *water R* and dilute to 20 ml with *water R*.

Optical rotation (*2.2.7*): – 0.10° to + 0.10°.

Dissolve 5.0 g in *dimethylformamide R* and dilute to 50.0 ml with the same solvent.

Impurity A. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 0.20 g in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 5 mg of *sulpiride impurity A CRS* (amisulpride impurity A) in *methanol R* and dilute to 25 ml with the same solvent. Dilute 2 ml of the solution to 20 ml with *methanol R*.

Reference solution (b). Dilute 1 ml of the test solution to 10 ml with reference solution (a).

Plate: *TLC silica gel G plate R*.

Mobile phase: the upper layer obtained after shaking a mixture of a 50 per cent *V/V* solution of *concentrated ammonia R, anhydrous ethanol R* and *di-isopropyl ether R* (10:25:65 *V/V/V*).

Application: 10 µl.

Development: over a path of 12 cm.

Drying: in air.

Detection: spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

System suitability: the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limit:

– *impurity A*: any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.10 g in 30 ml of *methanol R* and dilute to 100.0 ml with mobile phase B.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B. Dilute 1.0 ml of the solution to 25.0 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (b). Dissolve 5 mg of *amisulpride impurity B CRS* in 5 ml of the test solution and dilute to 50 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B. Dilute 1 ml of the solution to 10 ml with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm) with a carbon loading of 16 per cent, a specific surface area of 330 m^2/g and a pore size of 7.5 nm.

Mobile phase:

– *mobile phase A*: *methanol R*,

– *mobile phase B*: 0.7 g/l solution of *sodium octanesulphonate R* in a 0.25 per cent *V/V* solution of *dilute sulphuric acid R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	30 → 36	70 → 64
18 - 35	36 → 52	64 → 48
35 - 45	52	48
45 - 46	52 → 30	48 → 70
46 - 56	30	70

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µl.

System suitability: reference solution (b):

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

Limits:

– *any impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

– *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

Chlorides (*2.4.4*): maximum 200 ppm.

Shake 0.5 g with 30 ml of *water R* for 10 min. Filter. 15 ml of the filtrate complies with the test.

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 4.0 g by gently heating in 5 ml of *dilute acetic acid R*. Allow to cool and dilute to 20 ml with *water R*. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (2 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.

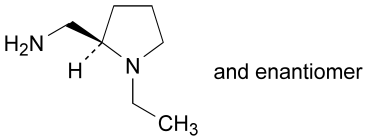
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g with shaking in a mixture of 5 ml of *acetic anhydride R* and 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

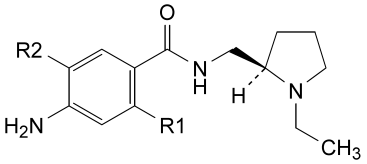
1 ml of *0.1 M perchloric acid* is equivalent to 36.95 mg of $C_{17}H_{27}N_3O_4S$.

IMPURITIES



and enantiomer

A. [(2*RS*)-1-ethylpyrrolidin-2-yl]methanamine,

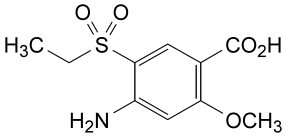


and enantiomer

B. R1 = OH, R2 = SO_2-CH_2-CH_3: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-hydroxybenzamide,

C. R1 = OCH_3, R2 = I: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-iodo-2-methoxybenzamide,

D. R1 = OCH_3, R2 = SO_2-CH_3: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-(methylsulphonyl)benzamide,



E. 4-amino-5-(ethylsulphonyl)-2-methoxybenzoic acid.