Limits:

- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);
- *sum of impurities other than A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1 per cent);
- *total*: maximum 2.0 per cent for the sum of the contents of all impurities;
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Impurity D. Liquid chromatography (*2.2.29*). *Carry out the test protected from light. Use shaking, not sonication or heat, to dissolve the reference substance and the substance to be examined.*

Test solution. Dissolve 0.100 g of the substance to be examined in *dimethyl sulphoxide R* and dilute to 100.0 ml with the same solvent.

Reference solution. Dissolve 3.0 mg of *aminoglutethimide impurity D CRS* in *dimethyl sulphoxide R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml with *dimethyl sulphoxide R*.

Column:

- *size*: *l* = 0.12 m, Ø = 4 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 0.285 g of *sodium edetate R* in *water R*, add 7.5 ml of *dilute acetic acid R* and 50 ml of *0.1 M potassium hydroxide* and dilute to 1000 ml with *water R*; adjust to pH 5.0 with *glacial acetic acid R*; mix 350 ml of this solution with 650 ml of *methanol R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 328 nm.

Injection: 10 µl.

System suitability: test solution:

- *number of theoretical plates*: minimum 3300, calculated for the principal peak;
- *mass distribution ratio*: 2.0 to 5.0 for the principal peak;
- *symmetry factor*: maximum 1.2 for the principal peak.

Limit:

- *impurity D*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (300 ppm).

Sulphates (*2.4.13*): maximum 500 ppm.

Dilute 6 ml of solution S to 15 ml with *distilled water R*.

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

Dissolve 2.0 g in 15 ml of *acetone R* and dilute to 20 ml with *water R*. 12 ml of the solution complies with test B. Prepare the reference solution using lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 15 ml of *acetone R* and 5 ml of *water 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.

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

ASSAY

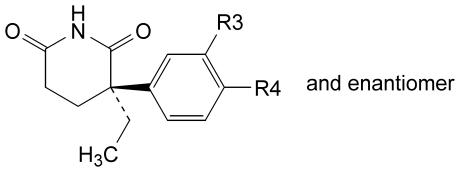
Dissolve 0.180 g in 50 ml of *anhydrous acetic acid R* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 23.23 mg of $C_{13}H_{16}N_2O_2$.

IMPURITIES

Specified impurities: A, D.

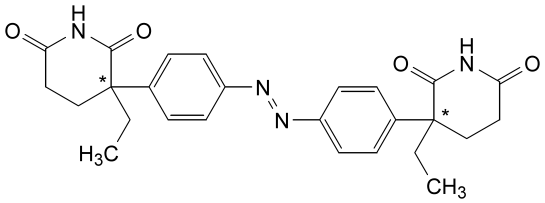
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *B, C.*



A. R3 = NH_2, R4 = H: (3*RS*)-3-(3-aminophenyl)-3-ethylpiperidine-2,6-dione (3-aminoglutethimide),

B. R3 = NO_2, R4 = H: (3*RS*)-3-ethyl-3-(3-nitrophenyl)-piperidine-2,6-dione,

C. R3 = H, R4 = NO_2: (3*RS*)-3-ethyl-3-(4-nitrophenyl)-piperidine-2,6-dione,

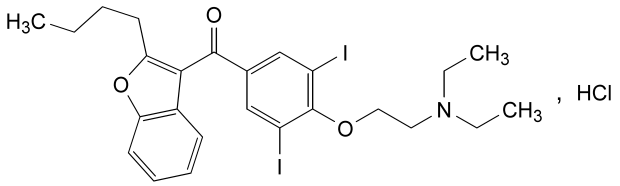


D. 3,3′-[diazenediylbis(4,1-phenylene)]bis(3-ethylpiperidine-2,6-dione) (azoglutethimide).

01/2008:0803

AMIODARONE HYDROCHLORIDE

Amiodaroni hydrochloridum



$C_{25}H_{30}ClI_2NO_3$ M_r 682

[199774-82-4]

DEFINITION

(2-Butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride.

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

CHARACTERS

Appearance: white or almost white, fine, crystalline powder.

Solubility: very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *amiodarone hydrochloride CRS*.

B. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution GY_5 or BY_5 (*2.2.2, Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 20 ml with the same solvent.

pH (*2.2.3*): 3.2 to 3.8.

Dissolve 1.0 g in *carbon dioxide-free water R*, heating at 80 °C, cool and dilute to 20 ml with the same solvent.

Impurity H. Thin-layer chromatography (*2.2.27*). *Prepare the solutions immediately before use and keep protected from bright light.*

Test solution. Dissolve 0.500 g of the substance to be examined in *methylene chloride R* and dilute to 5.0 ml with the same solvent.

Reference solution (a). Dissolve 10.0 mg of *(2-chloroethyl)diethylamine hydrochloride R* (impurity H) in *methylene chloride R* and dilute to 50.0 ml with the same solvent. Dilute 2.0 ml of this solution to 20.0 ml with *methylene chloride R*.

Reference solution (b). Mix 2.0 ml of the test solution and 2.0 ml of reference solution (a).

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

Mobile phase: *anhydrous formic acid R, methanol R, methylene chloride R* (5:10:85 *V/V/V*).

Application: 50 µl of the test solution and reference solution (a); 100 µl of reference solution (b).

Development: over 2/3 of the plate.

Drying: in a current of cold air.

Detection: spray with *potassium iodobismuthate solution R1* and then with *dilute hydrogen peroxide solution R*; examine immediately in daylight.

System suitability: reference solution (b):

– the spot due to impurity H is clearly visible.

Limit:

– *impurity H*: any spot with the same R_F as the spot due to impurity H in the chromatogram obtained with reference solution (b), is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.02 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution pH 4.9. To 800 ml of *water R* add 3.0 ml of *glacial acetic acid R*, adjust to pH 4.9 with *dilute ammonia R1* and dilute to 1000 ml with *water R*.

Test solution. Dissolve 0.125 g of the substance to be examined in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 25.0 ml with the same mixture of solvents.

Reference solution. Dissolve 5 mg of *amiodarone impurity D CRS*, 5 mg of *amiodarone impurity E CRS* and 5.0 mg of *amiodarone hydrochloride CRS* in *methanol R* and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of this solution to 20.0 ml with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

– *temperature*: 30 °C.

Mobile phase: buffer solution pH 4.9, *methanol R, acetonitrile R* (30:30:40 *V/V/V*).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µl.

Run time: twice the retention time of amiodarone.

Relative retention with reference to amiodarone (retention time = about 24 min): impurity A = about 0.26; impurity D = about 0.29; impurity E = about 0.37; impurity B = about 0.49; impurity C = about 0.55; impurity G = about 0.62; impurity F = about 0.69.

System suitability: reference solution:

– *resolution*: minimum 3.5 between the peaks due to impurities D and E.

Limits:

– *impurities A, B, C, D, E, F, G*: for each impurity, not more than the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.10 per cent);

– *total*: not more than 2.5 times the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.5 per cent);

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

Iodides: maximum 150 ppm.

Prepare the test and reference solutions simultaneously.

Solution A. Add 1.50 g of the substance to be examined to 40 ml of *water R* at 80 °C and shake until completely dissolved. Cool and dilute to 50.0 ml with *water R*.

Test solution. To 15.0 ml of solution A add 1.0 ml of *0.1 M hydrochloric acid* and 1.0 ml of *0.05 M potassium iodate*. Dilute to 20.0 ml with *water R*. Allow to stand protected from light for 4 h.

Reference solution. To 15.0 ml of solution A add 1.0 ml of *0.1 M hydrochloric acid*, 1.0 ml of an 88.2 mg/l solution of *potassium iodide R* and 1.0 ml of *0.05 M potassium iodate*. Dilute to 20.0 ml with *water R*. Allow to stand protected from light for 4 h.

Measure the absorbances (*2.2.25*) of the solutions at 420 nm, using a mixture of 15.0 ml of solution A and 1.0 ml of *0.1 M hydrochloric acid* diluted to 20.0 ml with *water R* as the compensation liquid. The absorbance of the test solution is not greater than half the absorbance of the reference solution.

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

1.0 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 at 50 °C at a pressure not exceeding 0.3 kPa for 4 h.

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

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.

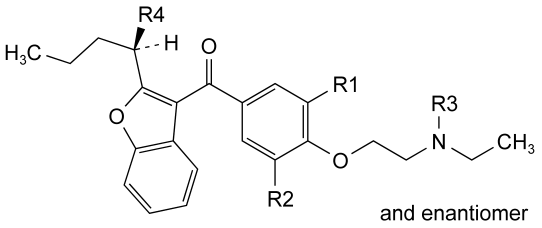
1 ml of *0.1 M sodium hydroxide* is equivalent to 68.18 mg of $C_{25}H_{30}ClI_2NO_3$.

STORAGE

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

IMPURITIES

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

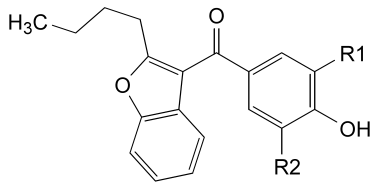


A. R1 = R2 = R4 = H, R3 = C_2H_5: (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]phenyl]methanone,

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,

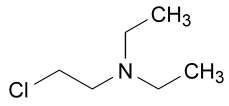
G. R1 = R2 = I, R3 = C_2H_5, R4 = OCH_3: [2-[(1*RS*)-1-methoxybutyl]benzofuran-3-yl][4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone,



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).

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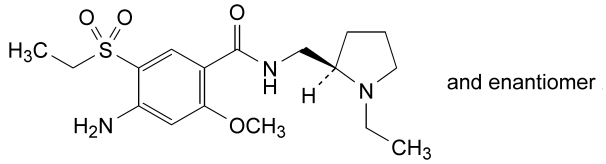
corrected 6.0

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.