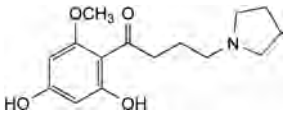
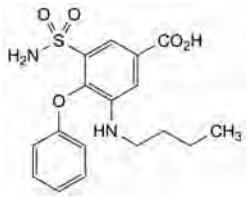


C. 1-(2,4-dihydroxy-6-methoxyphenyl)-4-(pyrrolidin-1-yl)butan-1-one.

01/2008:1076
corrected 8.4

BUMETANIDE

Bumetanidum



$C_{17}H_{20}N_2O_5S$ M_r 364.4
[28395-03-1]

DEFINITION

3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid.

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, soluble in acetone and in ethanol (96 per cent), slightly soluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (*5.9*).

mp: about 233 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *bumetanide 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 and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.1 g in a 6 g/L solution of *potassium hydroxide R* and dilute to 20 mL with the same solution.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 2 mg of *bumetanide impurity A CRS* and 2 mg of *bumetanide impurity B CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,
– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase: mix 70 volumes of *methanol R*, 25 volumes of *water for chromatography R* and 5 volumes of a 27.2 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with a 280 g/L solution of *potassium hydroxide R*; add *tetrahexylammonium bromide R* to this mixture to obtain a concentration of 2.17 g/L.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Run time: 5 times the retention time of bumetanide.

Relative retention with reference to bumetanide (retention time = about 6 min): impurity B = about 0.4; impurity A = about 0.6; impurity C = about 2.5; impurity D = about 4.4.

System suitability: reference solution (b):

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

Limits:

– *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),
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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).

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.

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

ASSAY

Dissolve 0.300 g in 50 mL of *alcohol R*. Add 0.1 mL of *phenol red solution R*. Titrate with *0.1 M sodium hydroxide* until a violet-red colour is obtained. Carry out a blank titration.

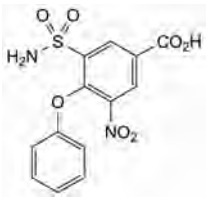
1 mL of *0.1 M sodium hydroxide* is equivalent to 36.44 mg of $C_{17}H_{20}N_2O_5S$.

STORAGE

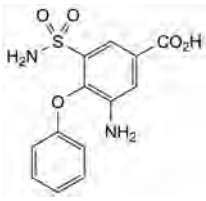
Protected from light.

IMPURITIES

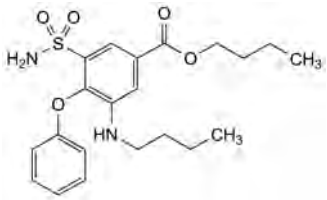
Specified impurities: A, B, C, D.



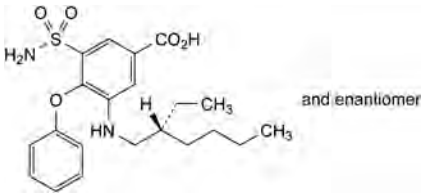
A. 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid,



B. 3-amino-4-phenoxy-5-sulfamoylbenzoic acid,



C. butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate,

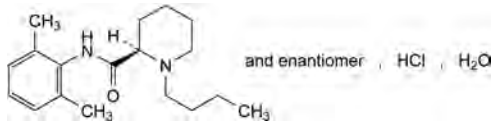


D. 3-[[(2*RS*)-2-ethylhexyl]amino]-4-phenoxy-5-sulfamoylbenzoic acid.

01/2017:0541
corrected 10.0

BUPIVACAINE HYDROCHLORIDE

Bupivacaini hydrochloridum



$C_{18}H_{29}ClN_2O,H_2O$ M_r 342.9
[73360-54-0]

DEFINITION

(2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: *A, D, E.*

Second identification: *B, C, D, E.*

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *bupivacaine hydrochloride CRS.*

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.
Reference solution. Dissolve 25 mg of *bupivacaine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.
Plate: *TLC silica gel G plate R.*
Mobile phase: *concentrated ammonia R*, *methanol R* (0.1:100 *V/V*).
Application: 5 µL.
Development: over a path of 10 cm.
Drying: in air.
Detection: spray with *dilute potassium iodobismuthate solution R.*
Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 0.1 g in 10 mL of *water R*, add 2 mL of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 15 mL, of *1,1-dimethylethyl methyl ether R*. Dry the combined upper layers over *anhydrous sodium sulfate R* and filter. Evaporate the filtrate, recrystallise the residue from *ethanol (90 per cent V/V) R* and dry under reduced pressure. The crystals melt (*2.2.14*) at 105 °C to 108 °C.

D. It gives reaction (a) of chlorides (*2.3.1*).

E. Optical rotation (see Tests).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S add 0.2 mL of *0.01 M sodium hydroxide*; the pH (*2.2.3*) is not less than 4.7. Add 0.4 mL of *0.01 M hydrochloric acid*; the pH is not greater than 4.7.

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

Dissolve 1.0 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances. Gas chromatography (*2.2.28*).

Internal standard solution. Dissolve 25 mg of *methyl behenate R* in *methylene chloride R* and dilute to 500 mL with the same solvent.

Test solution. Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer.

Reference solution (a). Dissolve 10 mg of the substance to be examined, 10 mg of *bupivacaine impurity B CRS* and 10 mg of *bupivacaine impurity E CRS* in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer and dilute to 20 mL with the internal standard solution.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the internal standard solution.

Reference solution (c). Dilute 5.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Reference solution (d). Dilute 1.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Column:
- *material*: fused silica;
- *size*: *l* = 30 m, Ø = 0.32 mm;
- *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas: *helium for chromatography R.*

Flow rate: 2.5 mL/min.

Split ratio: 1:12.

Temperature:

	Time (min)	Temperature (°C)
Column	0	180
	0 - 10	180 → 230
	10 - 15	230
Injection port		250
Detector		250

Detection: flame ionisation.