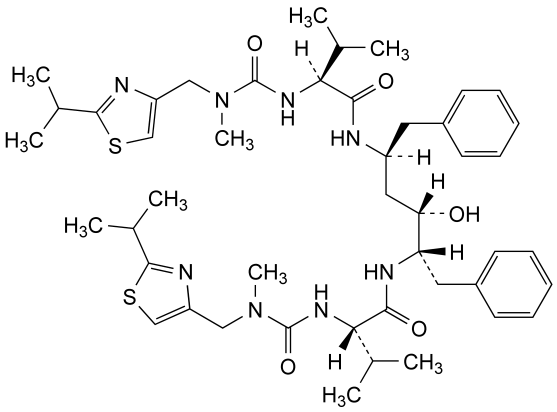
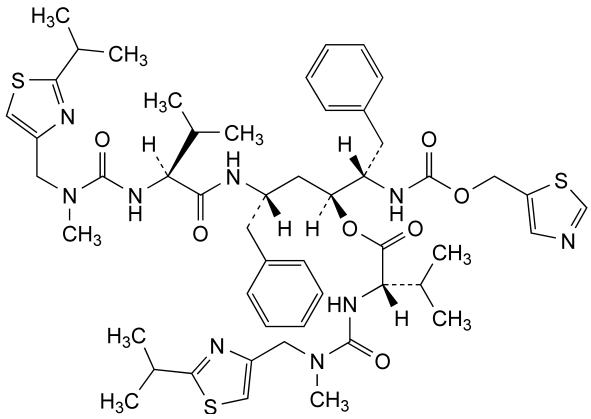


T. (2*S*)-*N*-[(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]-3-methyl-2-[[methyl[[2-(1-methylethyl)-thiazol-4-yl]methyl]carbamoyl]amino]butanamide,

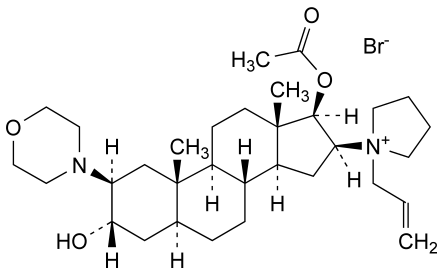


U. (1*S*,3*S*)-3-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]-butanoyl]amino]-4-phenyl-1-[(1*S*)-2-phenyl-1-[[(thiazol-5-ylmethoxy)carbonyl]amino]ethyl]butyl (2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoate.

**01/2008:1764**

# ROCURONIUM BROMIDE

## Rocuronii bromidum



$C_{32}H_{53}BrN_2O_4$ $M_r$ 610

DEFINITION

1-[17β-(Acetyloxy)-3α-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

*Content*: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

*Appearance*: almost white or pale yellow, slightly hygroscopic powder.

*Solubility*: freely soluble in water and in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *Ph. Eur. reference spectrum of rocuronium bromide.*

B. Solution S (see Tests) gives reaction (a) of bromides (*2.3.1*).

TESTS

**Solution S**. Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 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*).

**Specific optical rotation** (*2.2.7*): + 28.5 to + 32.0 (anhydrous substance).

Dissolve 0.250 g in a 5.15 g/l solution of *hydrochloric acid R* and dilute to 25.0 ml with the same solution.

**pH** (*2.2.3*): 8.9 to 9.5 for solution S.

**Related substances**. Liquid chromatography (*2.2.29*).

*Solvent mixture*: *water R, acetonitrile R1* (10:90 *V/V*).

*Test solution*. Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

*Reference solution (a)*. Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

*Reference solution (b)*. Dissolve 5 mg of *rocuronium for peak identification CRS* (containing impurities A, B, C, F, G and H) in the solvent mixture and dilute to 5 ml with the solvent mixture.

*Column*:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *silica gel for chromatography R* (5 µm),
– *temperature*: 30 °C.

*Mobile phase*: mix 100 volumes of a 4.53 g/l solution of *tetramethylammonium hydroxide R* adjusted to pH 7.4 with *phosphoric acid R* and 900 volumes of *acetonitrile R1*.

*Flow rate*: 2.0 ml/min.

*Detection*: spectrophotometer at 210 nm.

*Injection*: 5 µl of the test solution, reference solutions (a) and (b) and the solvent mixture (blank).

*Run time*: 2.5 times the retention time of rocuronium.

*Relative retention* with reference to rocuronium (retention time = about 9 min): impurity A = about 0.20; impurity G = about 0.44; impurity F = about 0.75; impurity B = about 0.80; impurity D = about 0.90; impurity H = about 0.95; impurity C = about 1.20; impurity E = about 1.53.

*System suitability*: reference solution (b):

– the chromatogram obtained is similar to the chromatogram supplied with *rocuronium for peak identification CRS*.

*Limits*:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.47; impurity F = 1.26; impurity G = 0.43; impurity H = 0.35;
- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *impurities B, C*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *impurities D, E, F, G, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: 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 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 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); disregard the peaks due to the blank and to bromide ion eluting just before impurity A.

**Chlorides**. Liquid chromatography (*2.2.29*).

*Test solution.* Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 20.0 ml with the same solvent.

*Reference solution (a).* Dissolve 0.824 g of *sodium chloride R* and 0.644 g of *sodium bromide R* in *water R* and dilute to 1000.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with *water R*.

*Reference solution (b).* Dissolve 0.824 g of *sodium chloride R* in *water R* and dilute to 1000.0 ml with the same solvent. Dilute 5.0 ml of the solution to 50.0 ml with *water R*. Dilute 2.0 ml of this solution to 50.0 ml with *water R*.

*Blank solution. Water R.*

*Precolumn*:

- *size*: *l* = 0.05 m, Ø = 4.0 mm,
- *stationary phase*: *anion exchange resin R* (13 µm).

*Column*:

- *size*: *l* = 0.25 m, Ø = 4.0 mm,
- *stationary phase*: *anion exchange resin R* (13 µm).

*Mobile phase*: a solution containing 0.063 g/l of *sodium hydrogen carbonate R* and 0.212 g/l of *anhydrous sodium carbonate R*.

*Flow rate*: 2.0 ml/min.

*Detection*: conductivity detector set at 100 µS/V and maintained at 30 °C.

Use a self-generating anion suppressor.

*Injection*: 25 µl.

*Retention times*: chloride = about 1.7 min; bromide = about 2.8 min.

*System suitability*: reference solution (a):

- *resolution*: minimum 2.5 between the peaks due to chloride and bromide.

*Limit*:

- *chlorides*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 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*.

**Water** (*2.5.12*): maximum 4.0 per cent, determined on 0.400 g.

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

ASSAY

Dissolve 0.400 g in 40 ml of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

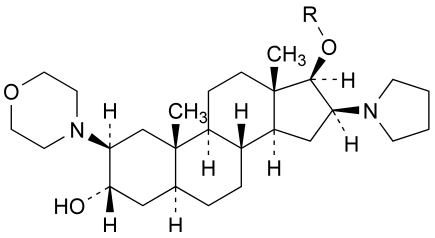
1 ml of *0.1 M perchloric acid* is equivalent to 60.97 mg of $C_{32}H_{53}BrN_2O_4$.

STORAGE

In an airtight container, protected from light.

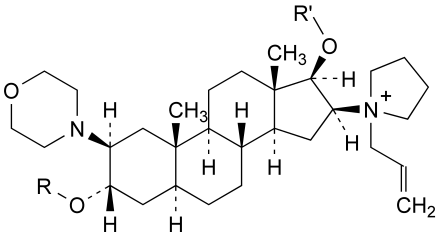
IMPURITIES

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



A. R = CO-$CH_3$: 3α-hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate,

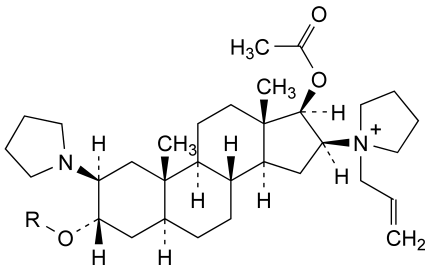
G. R = H: 2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstane-3α,17β-diol,



B. R = R′ = CO-$CH_3$: 1-[3α,17β-bis(acetyloxy)-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

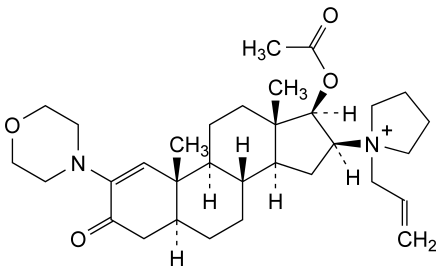
C. R = R′ = H: 1-[3α,17β-dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

D. R = CO-$CH_3$, R′ = H: 1-[3α-(acetyloxy)-17β-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,



E. R = H: 1-[17β-(acetyloxy)-3α-hydroxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

F. R = CO-$CH_3$: 1-[3α,17β-bis(acetyloxy)-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

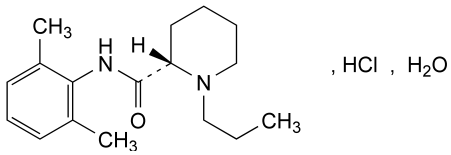


H. 1-[17β-(acetyloxy)-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

**01/2008:2335**

# ROPIVACAINE HYDROCHLORIDE MONOHYDRATE

## Ropivacaini hydrochloridum monohydricum



$C_{17}H_{27}ClN_2O,H_2O$ $M_r$ 328.9
[132112-35-7]

DEFINITION

(–)-(2*S*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate.

*Content*: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

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

*Solubility*: soluble in water and in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

Carry out either tests A, C, D or tests A, B, C.

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

B. Specific optical rotation (*2.2.7*): – 64.0 to – 74.0 (anhydrous substance).
Mix 2 ml of a 200 g/l solution of *sodium hydroxide R* and 30 ml of *water R* and dilute to 100.0 ml with *ethanol (96 per cent) R* (solution A). Dissolve 0.500 g of the substance to be examined in solution A and dilute to 50.0 ml with solution A.

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

D. Enantiomeric purity (see Tests).

TESTS

**Solution S**. Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25.0 ml with the same solvent.

**Appearance of solution**. Solution S is clear (*2.2.1*).

**pH** (*2.2.3*): 4.5 to 6.0 for solution S.

**Absorbance** (*2.2.25*): maximum 0.030 at 405 nm and maximum 0.025 at 436 nm, determined on solution S prepared immediately before use, with a path length of 5 cm and using *water R* as the compensation liquid.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 55 mg of the substance to be examined in the mobile phase and dilute to 20 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 5 mg of the substance to be examined and 5 mg of *bupivacaine hydrochloride CRS* (impurity A) in the mobile phase and dilute to 5 ml with the mobile phase. Dilute 1 ml of this solution to 100 ml with the mobile phase.

*Column*:
– *size*: *l* = 0.15 m, Ø = 3.9 mm;
– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 μm).

*Mobile phase*: mix 1.3 ml of a 138 g/l solution of *sodium dihydrogen phosphate R* and 32.5 ml of an 89 g/l solution of *disodium hydrogen phosphate R* and dilute to 1000 ml with *water R*; mix equal volumes of this solution (pH 8.0) and *acetonitrile R*.

*Flow rate*: 1.0 ml/min.

*Injection*: 20 μl.

*Detection*: spectrophotometer at 240 nm.

*Run time*: 2.5 times the retention time of ropivacaine.

*Relative retention* with reference to ropivacaine (retention time = about 6 min): impurity A = about 1.6.

*System suitability*: reference solution (b):
– *resolution*: minimum 6.0 between the peaks due to ropivacaine and impurity A.

*Limits*:
– *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

**Impurity H**. Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

*Test solution*. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

*Reference solution*. Dissolve 13.0 mg of *2,6-dimethylaniline hydrochloride R* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

*Retention time*: impurity H = about 2-3 min.

*Limit*:
– *impurity H*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (10 ppm).

**Enantiomeric purity**. Capillary electrophoresis (*2.2.47*): use the normalisation procedure.

*Test solution*. Dissolve 50 mg of the substance to be examined in *water R* and dilute to 25 ml with the same solvent.