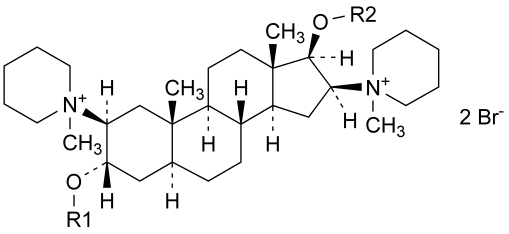
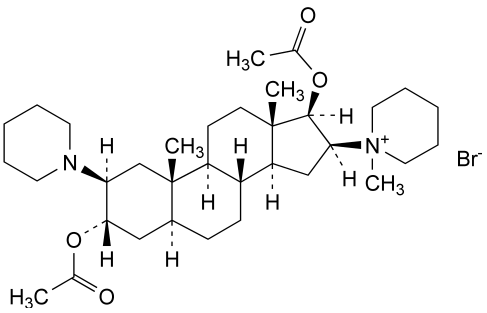
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



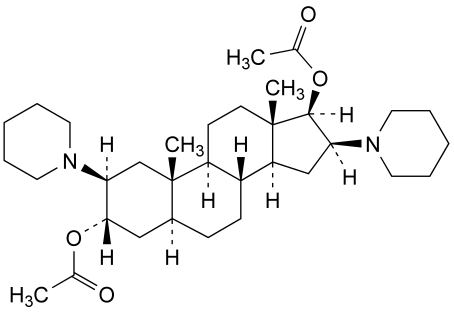
A. R1 = CO-CH_3, R2 = H: 1,1′-[3α-(acetyloxy)-17β-hydroxy-5α-androstane-2β,16β-diyl]bis(1-methylpiperidinium) dibromide (dacuronium bromide),

B. R1 = H, R2 = CO-CH_3: 1,1′-[17β-(acetyloxy)-3α-hydroxy-5α-androstane-2β,16β-diyl]bis(1-methylpiperidinium) dibromide,

C. R1 = R2 = H: 1,1′-(3α,17β-dihydroxy-5α-androstane-2β,16β-diyl)bis(1-methylpiperidinium) dibromide,



D. 1-[3α,17β-bis(acetyloxy)-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidinium bromide (vecuronium bromide),



E. 2β,16β-bis(piperidin-1-yl)-5α-androstane-3α,17β-diyl diacetate.

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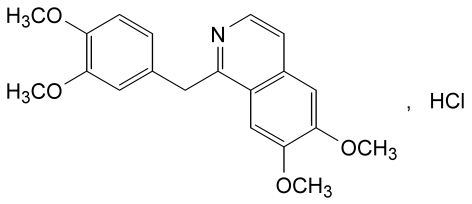
corrected 6.0

PAPAVERINE HYDROCHLORIDE

Papaverini hydrochloridum



$C_{20}H_{22}ClNO_4$ M_r 375.9
[61-25-6]

DEFINITION

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride.

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

CHARACTERS

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

Solubility: sparingly soluble in water, slightly soluble in alcohol.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *papaverine hydrochloride CRS*.

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

Test solution. Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 5 mg of *papaverine hydrochloride CRS* in *methanol R* and dilute to 10 ml with the same solvent.

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

Mobile phase: *diethylamine R, ethyl acetate R, toluene R* (10:20:70 *V/V/V*).

Application: 10 µl.

Development: over 2/3 of the plate.

Drying: at 100-105 °C for 2 h.

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.

C. To 10 ml of solution S (see Tests) add 5 ml of *ammonia R* dropwise and allow to stand for 10 min. The precipitate, washed and dried, melts (*2.2.14*) at 146 °C to 149 °C.

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

TESTS

Solution S. Dissolve 0.4 g in *carbon dioxide-free water R*, heating gently if necessary, and dilute to 20 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*): 3.0 to 4.0 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R*, mobile phase A (20:80 *V/V*).

Test solution. Dissolve 20.0 mg 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 solvent mixture.

Reference solution (b). Dissolve 12 mg of *noscapine CRS* in 1.0 ml of the test solution and dilute to 100.0 ml with the solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm,

– *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

– *mobile phase A*: 3.4 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *dilute phosphoric acid R*,

– *mobile phase B*: *acetonitrile R*,

– *mobile phase C*: *methanol R*,

Time (min)	Mobile phase A (per cent *V/V/V*)	Mobile phase B (per cent *V/V/V*)	Mobile phase C (per cent *V/V/V*)
0 - 5	85	5	10
5 - 12	85 → 60	5	10 → 35
12 - 20	60	5	35
20 - 24	60 → 40	5 → 20	35 → 40
24 - 27	40	20	40
27 - 32	40 → 85	20 → 5	40 → 10
32 - 40	85	5	10

Flow rate: 1 ml/min.

Detection: spectrophotometer at 238 nm.

Injection: 10 µl.

Relative retention with reference to papaverine (retention time = about 23.4 min): impurity E = about 0.7; impurity C = about 0.75; impurity B = about 0.8; impurity A = about 0.9; impurity F = about 1.1; impurity D = about 1.2.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity A and papaverine.

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 2.7; impurity D = 0.5; impurity A = 6.2;

– *any 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 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).

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 the residue from the test for loss on drying.

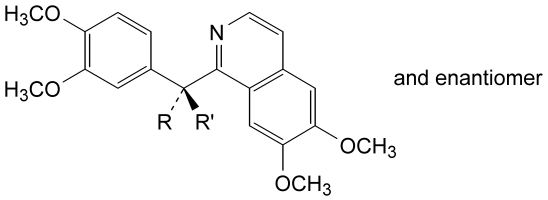
ASSAY

Dissolve 0.300 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 50 ml of *alcohol 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 37.59 mg of $C_{20}H_{22}ClNO_4$.

IMPURITIES

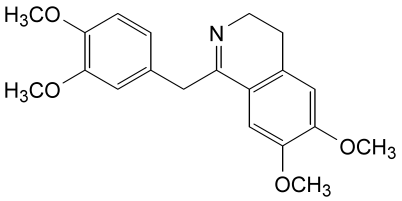
A. noscapine,



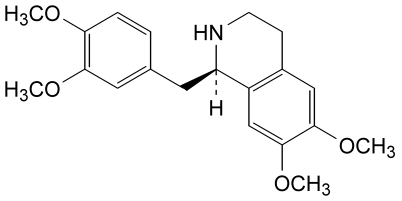
and enantiomer

B. R = OH, R′ = H: (*RS*)-(3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanol (papaverinol),

D. R + R′ = O: (3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (papaveraldine),

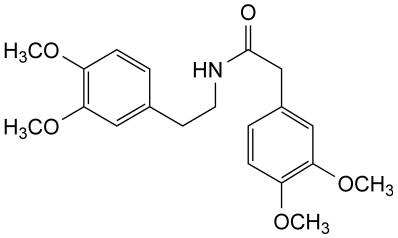


C. 1-(3,4−dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine),



and enantiomer

E. (1*RS*)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaverine),



F. 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]acetamide.