sulphate R, mix and allow to stand for 15 min. A stable, intense pink colour develops in the test solution. A brownish-yellow colour develops in the blank.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*).

Dissolve 0.6 g in *water R* and dilute to 20 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R, water R* (40:60 *V/V*).

Test solution (a). Dissolve 6 mg of the substance to be examined in the solvent mixture and dilute to 50 ml with the solvent mixture.

Test solution (b). Dissolve 6 mg of the substance to be examined in 30 ml of the solvent mixture. Add 5 ml of reference solution (b) and dilute to 50 ml with the solvent mixture.

Test solution (c). Dissolve 6 mg of *xanthydrol R1* and 6 mg of the substance to be examined in the solvent mixture, then dilute to 50 ml with the solvent mixture.

Reference solution (a). Dissolve 6 mg of *xanthydrol R1* in the solvent mixture and dilute to 50 ml with the solvent mixture.

Reference solution (b). Dilute 5 ml of reference solution (a) to 50 ml with the solvent mixture.

Column:

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

Mobile phase: mixture of equal volumes of *acetonitrile R* and of a solution containing 28 g/l of *sodium perchlorate R* and 11 g/l of *phosphoric acid R*, adjusted to pH 3.8 with *strong sodium hydroxide solution R* and then with *0.1 M sodium hydroxide*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 206 nm.

Injection: 20 µl of test solutions (a), (b), (c) and reference solution (a).

Run time: twice the retention time of propantheline.

System suitability: test solution (c):

– in the chromatogram obtained with test solution (a), there is no peak corresponding to the principal peak in the chromatogram obtained with reference solution (a);
– *resolution*: minimum 8.0 between the peaks due to propantheline and xanthydrol.

Limits: test solution (b):

– *any impurity*: for each impurity, not more than the area of the peak due to xanthydrol (1.0 per cent), and not more than one such peak has an area greater than or equal to 0.5 times the area of the peak due to xanthydrol (0.5 per cent);
– *disregard limit*: disregard any peak with a retention time relative to propantheline of less than 0.2 (bromide); disregard the peak due to xanthydrol.

Loss on drying (*2.2.32*): maximum 1.0 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 0.400 g in 50 ml of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* corresponds to 44.84 mg of $C_{23}H_{30}BrNO_3$.

STORAGE

In an airtight container.

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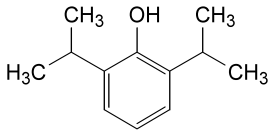
PROPOFOL

Propofolum



$C_{12}H_{18}O$ M_r 178.3
[2078-54-8]

DEFINITION

2,6-Bis(1-methylethyl)phenol.

Content: 98.0 per cent to 102.0 per cent.

This monograph applies to propofol prepared using distillation for purification.

CHARACTERS

Appearance: colourless or very light yellow, clear liquid.

Solubility: very slightly soluble in water, miscible with hexane and with methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *propofol CRS*.

TESTS

Refractive index (*2.2.6*): 1.5125 to 1.5145.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 1.00 g of the substance to be examined in *hexane R* and dilute to 10.0 ml with the same solvent.

Test solution (b). Dissolve 0.240 g of the substance to be examined in *hexane R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve 5 µl of the substance to be examined and 15 µl of *propofol impurity J CRS* in *hexane R* and dilute to 50.0 ml with the same solvent.

Reference solution (b). Dilute 0.1 ml of *propofol for peak identification CRS* (containing impurities E and G) to 1.0 ml with *hexane R*.

Reference solution (c). Dilute 1.0 ml of test solution (a) to 100.0 ml with *hexane R*. Dilute 1.0 ml of this solution to 10.0 ml with *hexane R*.

Reference solution (d). Dissolve 0.240 g of *propofol CRS* in *hexane R* and dilute to 100.0 ml with the same solvent.

Column:

– *size*: *l* = 0.20 m, Ø = 4.6 mm;

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

Mobile phase: *anhydrous ethanol R, acetonitrile R, hexane R* (1.0:7.5:990 *V/V/V*).

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 275 nm.

Injection: 10 µl of test solution (a) and reference solutions (a), (b) and (c).

Run time: 7 times the retention time of propofol.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G and E.

Relative retention with reference to propofol (retention time = about 3 min): impurity G = about 0.5; impurity I = about 0.6; impurity B = about 0.7; impurity N = about 2.3; impurity D = about 2.5; impurity P = about 2.9; impurity A = about 3.0; impurity C = about 3.4; impurity E = about 4.0; impurity F = about 5.8; impurity H = about 6.4.

System suitability: reference solution (a):

– *resolution*: minimum 4.0 between the peaks due to impurity J and propofol.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.25; impurity G = 5.0;

– *impurity G*: not more than twice the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.2 per cent);

– *impurity E*: not more than 0.1 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.01 per cent);

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.05 per cent);

– *total*: not more than 3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.3 per cent);

– *disregard limit*: 0.3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.03 per cent), except for impurity E.

Impurities J, K, L and O. Gas chromatography (*2.2.28*).

Test solution. Dissolve 40.0 mg of the substance to be examined in *methylene chloride R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *methylene chloride R*. Dilute 1.0 ml of this solution to 10.0 ml with *methylene chloride R*.

Reference solution (b). Dissolve 5 µl of *propofol impurity J CRS* (corresponding to 5 mg) in *methylene chloride R* and dilute to 100 ml with the same solvent. Dilute 1.0 ml of this solution to 25 ml with *methylene chloride R*.

Reference solution (c). Dissolve 4 mg of *propofol CRS* in reference solution (b) and dilute to 1 ml with the same solution.

Column:

– *material*: fused silica;

– *size*: *l* = 30 m, Ø = 0.32 mm;

– *stationary phase*: *polymethylphenylsiloxane R* (film thickness 0.5 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 1.7 ml/min.

Split ratio: 1:5.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	80
	3 - 25	80 → 210
	25 - 40	210
Injection port		100
Detector		270

Detection: flame ionisation.

Injection: 1 µl of the test solution and reference solutions (a) and (c).

Relative retention with reference to propofol (retention time = about 17 min): impurity K = about 0.76; impurity L = about 0.81; impurity J = about 1.01; impurity O = about 1.03.

System suitability: reference solution (c):

– *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity J, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to propofol.

Limits:

– *impurities J, K, L, O*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

ASSAY

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

Injection: test solution (b) and reference solution (d).

Calculate the percentage content of $C_{12}H_{18}O$ using the declared content of *propofol CRS*.

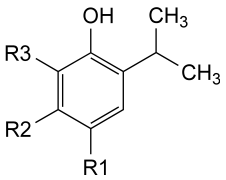
STORAGE

Protected from light under an inert gas.

IMPURITIES

Specified impurities: E, G, J, K, L, O.

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*): *A, B, C, D, F, H, I, N, P.*



A. R1 = $CH(CH_3)_2$, R2 = R3 = H: 2,4-bis(1-methylethyl)phenol,

B. R1 = R2 = H, R3 = $C(CH_3)=CH_2$: 2-(1-methylethenyl)-6-(1-methylethyl)phenol,

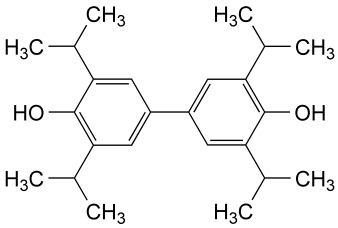
C. R1 = R2 = R3 = H: 2-(1-methylethyl)phenol,

D. R1 = R3 = H, R2 = $CH(CH_3)_2$: 2,5-bis(1-methylethyl)phenol,

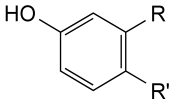
N. R1 = CO_2H, R2 = H, R3 = $CH(CH_3)_2$: 4-hydroxy-3,5-bis(1-methylethyl)benzoic acid,

O. R1 = R2 = H, R3 = CH_2-CH_2-CH_3: 2-(1-methylethyl)-6-propylphenol,

P. R1 = CO-O-$CH(CH_3)_2$, R2 = H, R3 = $CH(CH_3)_2$: 1-methylethyl 4-hydroxy-3,5-bis(1-methylethyl)benzoate,

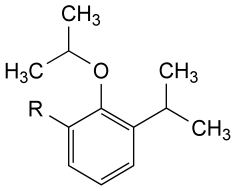


E. 3,3′,5,5′-tetrakis(1-methylethyl)biphenyl-4,4′-diol,



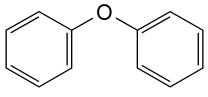
F. R = $CH(CH_3)_2$, R′ = H: 3-(1-methylethyl)phenol,

H. R = H, R′ = $CH(CH_3)_2$: 4-(1-methylethyl)phenol,

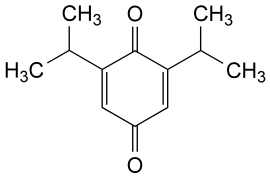


G. R = $CH(CH_3)_2$: 2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene,

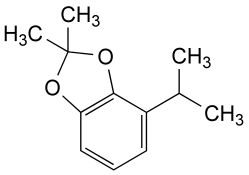
K. R = H: 1-(1-methylethoxy)-2-(1-methylethyl)benzene,



I. oxydibenzene,



J. 2,6-bis(1-methylethyl)benzene-1,4-dione,

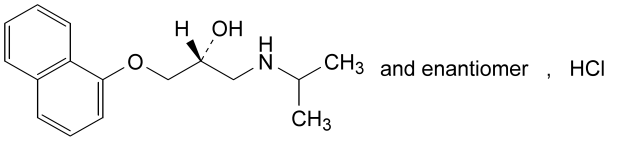


L. 2,2-dimethyl-4-(1-methylethyl)-1,3-benzodioxole.

01/2008:0568
corrected 6.0

PROPRANOLOL HYDROCHLORIDE

Propranololi hydrochloridum



$C_{16}H_{22}ClNO_2$ M_r 295.8
[318-98-9]

DEFINITION

(2*RS*)-1-[(1-Methylethyl)amino]-3-(naphthalen-1-yloxy)-propan-2-ol hydrochloride.

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

CHARACTERS

Appearance: white or almost white powder.

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

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 163 °C to 166 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *propranolol hydrochloride CRS.*

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

Test solution. Dissolve 10 mg of the substance to be examined in 1 ml of *methanol R.*

Reference solution. Dissolve 10 mg of *propranolol hydrochloride CRS* in 1 ml of *methanol R.*

Plate: *TLC silica gel G plate R.*

Mobile phase: *concentrated ammonia R1, methanol R* (1:99 *V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: at 100-105 °C.

Detection: spray with *anisaldehyde solution R* and heat at 100-105 °C until the colour of the spots reaches maximum intensity (10-15 min).

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.

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