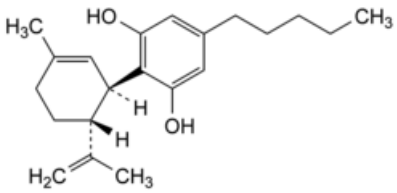
Edition: BP 2025 (Ph. Eur. 11.6 update)

Cannabidiol

General Notices

(Ph. Eur. monograph 3151)



$C_{21}H_{30}O_2$ 314.5 *13956-29-1*

Action and use

Cannabinoid receptor agonist; adjunctive therapy used in the treatment of seizures (epilepsy).

Ph Eur

DEFINITION

(1′*R*,2′*R*)-5′-Methyl-4-pentyl-2′-(prop-1-en-2-yl)-1′,2′,3′,4′-tetrahydro[1,1′-biphenyl]-2,6-diol.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It is isolated from the *Cannabis sativa* L. plant.

CHARACTERS

Appearance

White to pale yellow powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methanol, soluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cannabidiol CRS*.

B. Specific optical rotation (see Tests).

TESTS

Specific optical rotation (*2.2.7*)

-135.0 to -128.0 (anhydrous substance).

Dissolve 0.200 g in *ethanol (96 per cent) R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 15.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 7.5 mg of *cannabidiol for system suitability CRS* (containing impurities A, B, C and E) in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 15.0 mg of *cannabidiol CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (d) Transfer 1 mL of reference solution (c) to a vial and add 25 µL of a 103 g/L solution of *hydrochloric acid R*. Keep at room temperature for 2 h before injection to allow the *in situ* formation of impurity D.

Reference solution (e) Dissolve the contents of a vial of *cannabidiol impurity J CRS* in 1 mL of *methanol R*.

Reference solution (f) Dilute 2.0 mL of reference solution (c) to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped, charged surface, ethylene-bridged phenylhexylsilyl silica gel for chromatography (hybrid material) R* (2.5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: a 1 g/L solution of *formic acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	50	50
1 - 14	50 → 35	50 → 65
14 - 24	35 → 5	65 → 95

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 275 nm.

Autosampler Set at 5 °C.

Injection 10 µL of test solution (a) and reference solutions (a), (b), (d) and (e).

Identification of impurities Use the chromatogram supplied with *cannabidiol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity J.

Relative retention With reference to cannabidiol (retention time = about 12 min): impurity J = about 0.49; impurity A = about 0.72; impurity B = about 0.85; impurity C = about 1.15; impurity D = about 1.21; impurity E = about 1.26.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to cannabidiol and impurity C.

Calculation of percentage contents:

— *correction factors*: multiply the peak area of the impurity by its correction factor: impurity C = 0.05; impurity E = 0.08;

— for each impurity, use the concentration of the substance to be examined in reference solution (a).

Limits:

— *impurity A*: maximum 0.80 per cent;

— *impurity B*: maximum 0.50 per cent;

— *impurities C, E and J*: for each impurity, maximum 0.15 per cent;

— *impurity D*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent.

Dissolve 50.0 mg in *anhydrous methanol R* and dilute to 2.0 mL with the same solvent. Inject 0.8 mL of the solution through the septum.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent determined on 1.0 g.

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 (f).

Calculate the percentage content of $C_{21}H_{30}O_2$ taking into account the assigned content of *cannabidiol CRS*.

STORAGE

In an airtight container, protected from light.

LABELLING

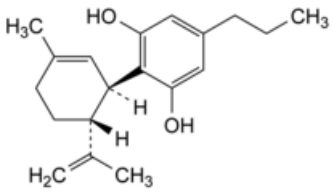
The label states the origin of the substance:

— isolated from the *Cannabis sativa* L. plant.

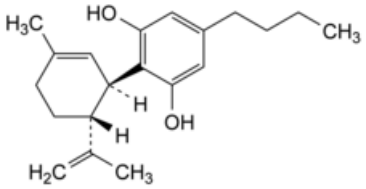
IMPURITIES

Specified impurities A, B, C, D, E, J.

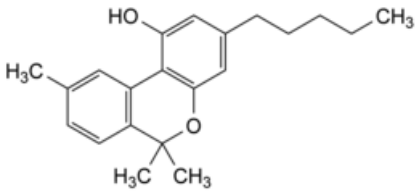
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



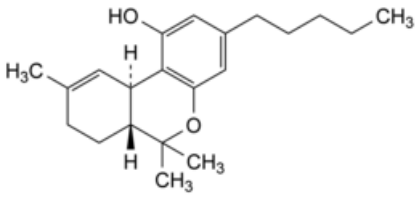
A. (1′*R*,2′*R*)-5′-methyl-2′-(prop-1-en-2-yl)-4-propyl-1′,2′,3′,4′-tetrahydro[1,1′-biphenyl]-2,6-diol (cannabidivarin),



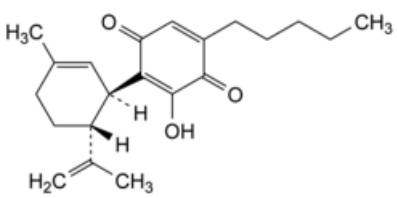
B. (1′*R*,2′*R*)-4-butyl-5′-methyl-2′-(prop-1-en-2-yl)-1′,2′,3′,4′-tetrahydro[1,1′-biphenyl]-2,6-diol (cannabidibutol),



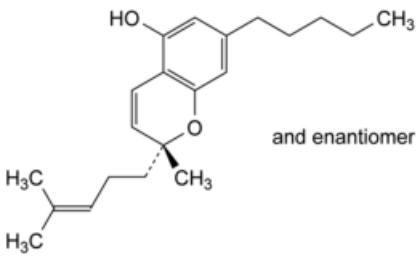
C. 6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (cannabinol),



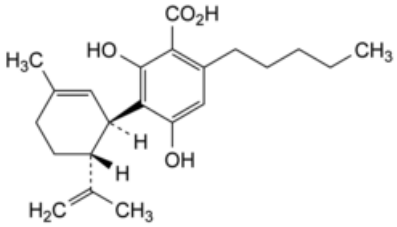
D. (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol (Δ^9-tetrahydrocannabinol, dronabinol),



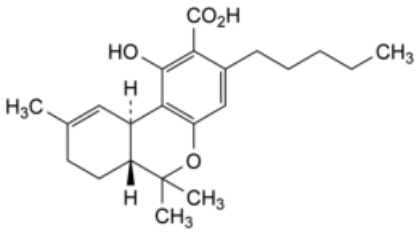
E. (1′*R*,6′*R*)-6-hydroxy-3′-methyl-4-pentyl-6′-(prop-1-en-2-yl)[[1,1′-bi(cyclohexane)]-2′,3,6-triene]-2,5-dione,



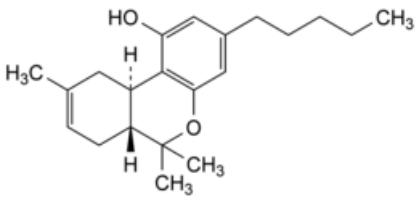
F. (2*RS*)-2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2*H*-1-benzopyran-5-ol (cannabichromene),



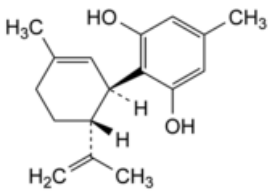
G. (1′*R*,2′*R*)-2,6-dihydroxy-5′-methyl-4-pentyl-2′-(prop-1-en-2-yl)-1′,2′,3′,4′-tetrahydro[1,1′-biphenyl]-3-carboxylic acid (cannabidiolic acid),



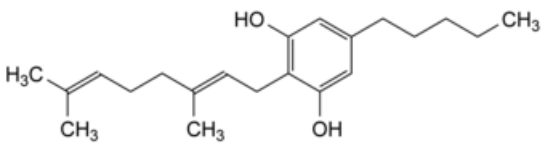
H. (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-2-carboxylic acid (Δ^9-tetrahydrocannabinolic acid),



I. (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol (Δ^8-tetrahydrocannabinol),



J. (1′*R*,2′*R*)-4,5′-dimethyl-2′-(prop-1-en-2-yl)-1′,2′,3′,4′-tetrahydro[1,1′-biphenyl]-2,6-diol (cannabidiorcol),



K. 2-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-5-pentylbenzene-1,3-diol (cannabigerol).

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