

Vitamin A

1. Chemical and physical characteristics

The general characteristics of retinol, retinyl acetate, retinyl palmitate and β -retinal have been obtained from the following: Beilstein (Boit, 1966); *Directory of Chemical Producers* (MDL Information Systems, 1998); *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed. (Kroschwitz, 1998); Kelloff *et al.* (1994a); *Martindale. The Extra Pharmacopoeia* (Reynolds, 1989); *The Merck Index*, 12th ed. (Budavari, 1996); and the *Physicians' Desk Reference* (1997).

1.1 Retinol

1.1.1 Name

Chemical Abstracts Services Registry Number
68-26-8

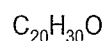
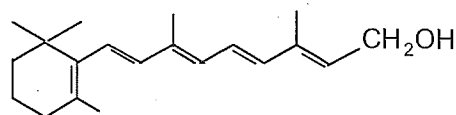
Chemical Abstracts Primary Name
Retinol

IUPAC Systematic Name
(All-*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol

Synonyms

All-*trans*-retinol; anti-infective vitamin; anti-xerophthalmic vitamin; 15-*apo*- β -caroten-15-ol; axerol; axerophthol; axerophtholum; biosterol; (*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenol; (*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)-2,4,6,8-nonatetraenol; fat-soluble A (obsolete); (*E*)-9-hydroxy-3,7-dimethyl-9-(2,6,6-trimethylcyclohexenyl)-1,3,5,7-nonatetraene; lard factor; oleovitamin A; ophthalamine (obsolete); *trans*-retinol; 2-*trans*,4-*trans*,6-*trans*,8-*trans*-retinol; vitamin A; vitamin A₁; vitamin A₁ alcohol; vitamin A alcohol; vitaminum A.

1.1.2 Structural and molecular formulae and relative molecular mass



Relative molecular mass: 286.46

1.1.3 Physical and chemical properties

Description

Pale yellow prisms

Melting-point

62–64°C (yellow prisms from ethyl formate, petroleum ether, propylene oxide)

Solubility

Soluble in most organic solvents (acetone, chloroform, dimethyl sulfoxide, ether, ethanol, hexane, isopropanol, methanol) and in fats and mineral oils (2.5 mol/L) (Boit, 1966); practically insoluble in water (0.06 μ mol/L) (Szuts & Harosi, 1991) and glycerol.

Spectroscopy

Double-bond isomers of retinol do not show differences in their infrared spectra, which are briefly mentioned in the review by Frickel (1984) and more extensively covered in that by Isler *et al.* (1971). The ultraviolet (UV) absorption spectrum in ethanol has λ_{\max} at 325 nm; $E_{1\text{cm}}^{1\%} = 1835$ (Tee, 1992). Retinol exhibits yellow-green fluorescence at 510 nm after excitation at 327 nm and at 470 nm after excitation at 325 nm. The infrared (IR) and proton magnetic resonance (¹H-NMR) spectra of retinol can be found in the relevant Aldrich Library volumes (Pouchert, 1985; Pouchert & Behnke, 1993).

Stability

Photo-induced bond isomerization from *trans* to *cis* gives the other known retinol isomers: 11-*cis* (neo b), 13-*cis* (neo a), 9,13-di-*cis* (iso b), 9-*cis* (iso a), and 11,13-di-*cis* (neo c) (Tee, 1992). Particularly in oil solution, retinol can be protected from isomerization by preventing exposure to UV and sunlight. Bond isomerization can also be caused by heat and iodine. High levels of illumination can induce polymerization. Retinol is sensitive to oxygen and is optimally stored at below 4°C under an inert gas (argon or nitrogen) or in the presence of an antioxidant, such as butylated hydroxytoluene. Heat and trace metals accelerate retinol decomposition by oxygen and light (Kroschwitz, 1998). Retinol is unstable to acids, which cause bond rearrangement to retrovitamin A, isomerization, and dehydration to anhydrovitamin A, sometimes followed by solvent addition; it is also unstable to alkali in the presence of oxygen (Tee, 1992). Unlike the palmitate ester, the alcohol and its acetate can bind strongly to polyvinyl chloride in plastics used for administration.

1.1.4 Technical products

Commercial preparations of retinol may contain antioxidants (low levels of butylated hydroxyanisole and butylated hydroxytoluene, dispersants and antimicrobial agents when diluted with edible oils or solid dispersants (Polysorbate 20). One international unit (IU) of vitamin A is defined as 0.3 µg of pure all-*trans*-retinol.

The major producers of vitamin A are BASF AG (Germany), BASF Corp. (USA), BASF Mexicana (Mexico), Bayer AG (Germany), Gaveteco S.A.I.C.I. e I. (Argentina), Hoffmann-La Roche AG (Germany) and Rhone-Poulenc Animal Nutrition (France).

1.2 Retinyl acetate

1.2.1 Name

Chemical Abstracts Services Registry Number
127-47-9

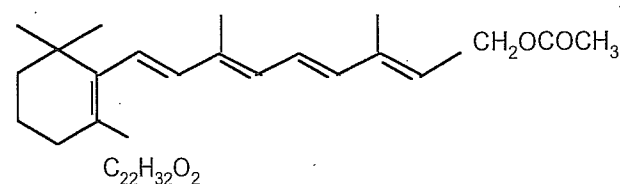
Chemical Abstracts Primary Name
Retinyl acetate
IUPAC Systematic Name

(*E*)-9-Acetyl-3,7-dimethyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenol

Synonyms

Acetic acid (*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenyl ester; acetic acid retinyl ester; all-*trans*-retinyl acetate; all-*trans*-retinol acetate; *O*-acetoxy-all-*trans*-retinol; *O*-acetyl-all-*trans*-retinol; retinyl acetate; 2-*trans*,4-*trans*,6-*trans*,8-*trans*-retinol acetate; 2-*trans*,4-*trans*,6-*trans*,8-*trans*-retinyl acetate; vitamin A acetate.

1.2.2 Structural and molecular formulae and relative molecular mass



Relative molecular mass: 328.5

1.2.3 Physical and chemical properties

Description

Pale yellow prisms or yellow supercooled, viscous liquid

Melting point

57–58°C

Solubility

Soluble in most organic solvents (acetone, chloroform, ethanol, isopropanol) and in fats and oils (750 g/100 mL); insoluble in water and glycerol.

Spectroscopy

UV-visible: λ_{\max} 326 nm (in ethanol);
 $E_{1\text{ cm}}^{1\%}$ 1550.

Fluorescence

Emission λ_{\max} at 470 nm for excitation at 325 nm

Stability

More stable than retinol. For stability in crystalline form and in solution, see Guerrant

et al. (1948); for stability to hydrolysis in ethanolic sodium hydroxide at 40° and 60°C, see Isler *et al.* (1949). Store at below 4°C.

1.2.4 Technical products

Activity is based on high-performance liquid chromatographic comparison with the international standard. The international unit (IU) was defined by the WHO Expert Committee on Biological Standardization as the activity of 0.344 µg of pure all-*trans*-retinyl acetate. Synthetic material may be sold dispersed in a corn starch–gelatin matrix (Sigma, USA) or in gelatin, sucrose, peanut oil, and calcium phosphate-containing butylated hydroxyanisole and butylated hydroxytoluene (USB, USA), and in pure form (2 800 000 IU/g, Sigma). Major producers are BASF AG (Germany), F. Hoffman-La Roche AG (Germany) and Roche AG (Switzerland). In one pharmaceutical source (Materna prenatal tablets; Lederle, USA), retinyl acetate is combined with β-carotene and vitamins D, E, B₁, B₂, B₆, B₁₂, biotin, pantothenic acid and minerals.

1.3 Retinyl palmitate

1.3.1 Name

Chemical Abstracts Services Registry Number
79-81-2

Chemical Abstracts Primary Name
Retinol hexadecanoate

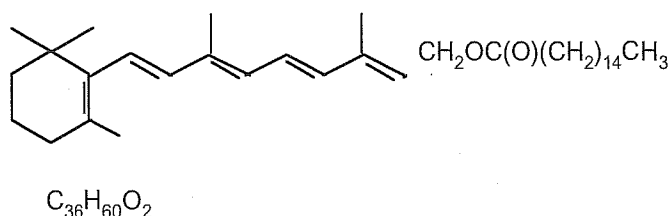
IUPAC Systematic Name

(*E*)-3,7-Dimethyl-9-*O*-palmitoyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenol

Synonyms

Palmitic acid (*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenyl ester; palmitic acid retinyl ester; *O*-palmitoyl-all-*trans*-retinol; *O*-palmitoyl-retinol; *O*-palmitoyl-retinol; retinyl palmitate; 2-*trans*,4-*trans*,6-*trans*,8-*trans*-retinyl palmitate; 2-*trans*,4-*trans*,6-*trans*,8-*trans*-retinol palmitate; *trans*-retinol palmitate; *trans*-retinyl palmitate; vitamin A palmitate.

1.3.2 Structural and molecular formulae and relative molecular mass



Relative molecular mass: 524.8

1.3.3 Physical and chemical properties

Description

Yellow, crystalline or amorphous powder, n_D^{20} 1.5558 (Tee, 1992)

Melting-point

27–29°C (Tee, 1992)

Solubility

Soluble in most organic solvents (ethanol, isopropanol, chloroform, acetone) and in fats and oils insoluble in water and glycerol.

Spectroscopy

UV-visible: λ_{max} 325–328 nm (in ethanol);
 $E_{1\text{ cm}}^{1\%}$ 940–975

Fluorescence

Emission λ_{max} at 470 nm for excitation at 325 nm

Stability

More stable than retinol to oxidation in air; rate of hydrolysis in ethanolic sodium hydroxide was reported by Isler *et al.* (1949). Store at below 4°C.

1.3.4 Technical products

One IU of vitamin A is contained in 0.55 µg of pure all-*trans*-retinyl palmitate. Major producers of retinyl palmitate are BASF AG (Germany), BASF Mexicana, S.A. de C.V. (Mexico), F. Hoffman-La Roche AG (Switzerland) and Piramal Health-care Limited (India). A pharmaceutical source is Aquasol A (capsules or the parental form is water-miscible by solubilization in polysorbate 80; Carlson

Laboratories, USA). Retinyl palmitate is also available in a corn starch–gelatin matrix containing butylated hydroxyanisole and butylated hydroxytoluene, in a water-dispersible starch–gelatin matrix containing butylated hydroxyanisole and butylated hydroxytoluene, in a mixture of acacia, lactose, coconut oil, butylated hydroxytoluene, sodium benzoate, sorbic acid, and silicon dioxide, or in corn oil (USB, USA).

1.4 Retinal

1.4.1 Name

Chemical Abstracts Service Registry Number
116-31-4

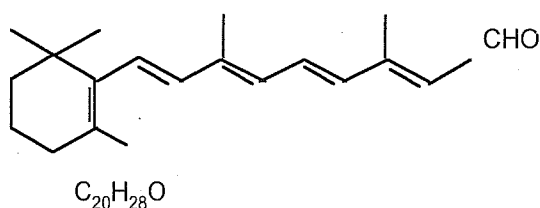
Chemical Abstracts Primary Name
Retinal

IUPAC Systematic Name
(All-*E*)-3,7-Dimethyl-2-(2,6,6-trimethyl-1-cyclohexen-1-yl)2,4,6,8-nonatetraenol

Synonyms

All-*trans*-retinal, axerophthal, retinaldehyde, retinene, vitamin A aldehyde

1.4.2 Structural and molecular formulae and relative molecular mass



Relative molecular mass 284.4

1.4.3 Physical and chemical properties

Description

Orange crystals (from petroleum ether)

Melting point

64–65°C

Solubility

Soluble in ethanol, chloroform, cyclohexane,

petroleum ether and oils; virtually insoluble in water.

Spectroscopy

IR (Rockley *et al.*, 1986); NMR (Patel, 1969)

UV-visible

λ_{\max} 383 nm (E 4.288 $\times 10^4$ in ethanol); λ_{\max} 368 nm (E 4.88 $\times 10^4$ in hexane) (Hubbard *et al.*, 1971)

Stability

Sensitive to light and oxygen. Store under an inert gas (argon or nitrogen) at < 4°C.

Commercial sources

Retinal can be obtained from the following suppliers: Sigma (USA), Crescent Chemical Co. (USA), Nacalia Tesque, Inc. (Japan) and Kanto Chemicals Co. (Japan).

1.5 Retinoic acid

1.5.1 Name

Chemical Abstracts Services Registry Number
302-79-4

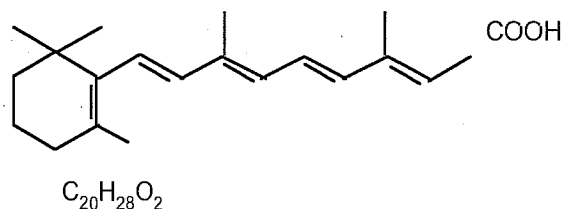
Chemical Abstracts Primary Name
Retinoic acid

IUPAC Systematic Name
All-*trans*-retinoic acid

Synonyms

(All-*E*)-3,7-dimethyl-9-(2,2,6-trimethylcyclohexenyl)nona-2,4,6,8-tetraenoic acid, *trans*-retinoic acid, tretinoin, vitamin A acid, vitamin A₁ acid.

1.5.2 Structural and molecular formulae and relative molecular mass



Relative molecular mass 300.45

1.5.3 Physical and chemical properties

Description

Yellow crystals

Melting-point

180–182°C (Tee, 1992).

Solubility

Soluble in most organic solvents, fats, and oils; low solubility in water (0.21 $\mu\text{mol/L}$) (Szuts & Harosi, 1991)

Spectroscopy

UV-visible: λ_{max} 350 (ethanol), $E_{1\text{ cm}}^{1\%}$ 1510 (Tee, 1992).

Stability

Unstable to light, oxygen and heat, but less so than retinol. Store under inert gas at below 4°C or in the presence of an antioxidant.