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PROVISIONAL

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

and

INTERNATIONAL UNION OF BIOCHEMISTRY

JOINT COMMISSION ON BIOCHEMICAL NOMENCLATURE*

NOMENCLATURE OF RETINOIDS

Comments on these recommendations are welcome and should be sent within 8 months from April 1983 to the Secretary of the Commission

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Comments from the viewpoint of languages other than English are especially encouraged. These may have special significance regarding the publication in various countries of translations of the nomenclature eventually approved by IUPAC.

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PROVISIONAL

IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN)

Nomenclature of Retinoids

Recommendations 1981

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PREAMBLE

Funk [1] suggested in 1912 the term 'vitamine' to describe a growth factor present in food which was essential for life. It later became clear that there was more than one growth factor, and McCollum [2] divided them into two classes, 'fat-soluble A' and 'water-soluble B'. Objecting to the chemical implications of the suffix '-ine', Drummond [3] suggested deletion of the final 'e', renamed McCollum's two groups vitamin A and vitamin B, and proposed that further members of this series be called vitamin C, vitamin D, etc.

Document of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), whose members are: P. Karlson (chairman), H. B. F. Dixon, C. Liébecq (as chairman of the IUB Committee of Editors of Biochemical Journals), K. L. Loening, G. P. Moss, J. Reedijk, S. F. Velick, and J. F. G. Vliegenthart. JCBN thanks other members of the Nomenclature Committee of IUB (H. Bielka and N. Sharon) for consultation. Comments and suggestions for future revisions of these recommendations may be sent to its secretary, H. B. F. Dixon, University Department of Biochemistry, Tennis Court Road, Cambridge, England CB2 1QW, or to any member.

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In 1934 Wald [4] isolated from animal retina a substance he called retinene. Morton [5] suggested that this compound was the aldehyde of vitamin A, and [6] called it retinaldehyde (rather than retinal). The correct structure of vitamin A was deduced in 1931 by Karrer [7] who proposed [8] the name axerophthol (*Axerophtol* in German), based on its action in preventing the eye disease xerophthalmia. A second vitamin A, isolated by Morton and others, was called vitamin A_2 [9].

Recommendations for the nomenclature of the vitamins were published by IUPAC in 1960 [10]. These included names for the three parent compounds – retinol, retinal and retinoic acid – as well as for their 3-dehydro analogues. A revised and enlarged version of these recommendations was published by the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) in 1965 [11]. With the publication by the IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC) and CBN of the 'Nomenclature of carotenoids' [13] and by CNOC of 'Section F' (Natural products and related compounds) [14] of the 'Nomenclature of Organic Chemistry' [15] it was decided by JCBN that a separate document should be published extending section M-1 of the 1965 document. The present recommendations are based on drafts prepared by G. P. Moss in consultation with several active workers in the field and with CNOC.

RECOMMENDATIONS

Ret-1. CLASS OF COMPOUNDS

Retinoids are a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. All retinoids may be formally derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional group at the terminus of the acyclic portion. To avoid confusion with previously used names in this field no parent hydrocarbon is named (see Ret-4.1).

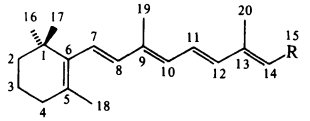
1.1. *Vitamin A*

The term vitamin A should be used as the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol. This term should be used in derived terms such as vitamin A activity, vitamin A deficiency, vitamin A antagonist [16].

Ret-2. STEREOPARENTS

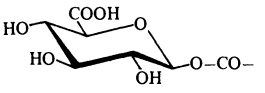
A stereoparent is a parent compound whose name implies stereochemistry, which will not need to be stated explicitly.

It is convenient to omit the explicit representation of C and H atoms in the skeletal formulae of retinoids as follows:



(*1*) R = CH_2OH
(*2*) R = CHO
(*3*) R = CO_2H
(*4*) R = CH_3
(*5*) R = CH_2OCOCH_3
(*6*) R = CH_2NH_2
(*7*) R = CH=NOH
(*8*) R = $CH=N[CH_2]_4CHNH_2CO_2H$
(*9*) R = $CO_2C_2H_5$

(*10*) R- =



2.1. *Retinol*

The compound (*1*) (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraen-1-ol[1], also known as vitamin A, vitamin A alcohol, vitamin A_1, vitamin A_1 alcohol, axerophthol or axerol, should be designated retinol[2].

2.2. *Retinal*

The compound (*2*) also known as vitamin A aldehyde, vitamin A_1 aldehyde, retinene or retinene$_1$ should be designated retinal[3] or, if liable to be confused with the adjective retinal (pertaining to the retina), retinaldehyde[4].

2.3. *Retinoic Acid*

The compound (*3*) also known as tretinoin[2], vitamin A acid or vitamin A_1 acid should be designated retinoic acid.

Ret-3. NUMBERING

The basic system of numbering is that shown in structures (*1*) to (*10*). This follows the system outlined in the carotenoid rules in Rule Car-4 and Rule Car-12.4 [13].

Ret-4. MODIFICATION OF STEREOPARENT

4.1. *Basic Hydrocarbon*

The hydrocarbon (*4*), also known as axerophthene, should be designated deoxyretinol[5]. This hydrocarbon cannot be considered as the stereoparent for the stem 'retin-' as it would then need to be called retinene, a name already used as a misleading synonym for retinal (Ret-2.2). A name such as retinane is inappropriate as it would imply a saturated hydrocarbon (Rule F-2.3 in [14]).

[1] The numbering system of the systematic name is different from above. See Ret-3.
[2] WHO-approved nonproprietary names.
[3] Recommended for chemical usage.
[4] Recommended for nutritional usage [16].
[5] The prefix deoxy may be either detachable or non-detachable (see Rule C-16.11 [15]). In this document it is treated as a non-detachable prefix and, so that the locant 15 is not needed, it is always placed next to the stem name (cf. Rule C-16.32 [15]).

4.2. *Change of the Functional Group*

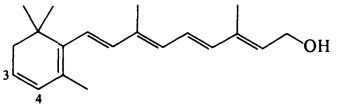
4.2.1. Functional substitution at the 15 position of the basic hydrocarbon is denoted by the use of the group names retinyl (R is CH_2-) or retinylidene (R is CH=), with retention of the original numbering of the basic hydrocarbon. For example (*5*) is retinyl acetate and (*6*) is retinylamine.

4.2.2. A compound derived from retinal is named either as an aldehyde derivative (following Rule C-842, Rule C-922 or Rule C-982 in [15]), or as a compound substituted by the bivalent radical retinylidene (Rule A-4.1 in [15]). For example (*7*) is retinal oxime and (*8*) is N^6-retinylidene-L-lysine.

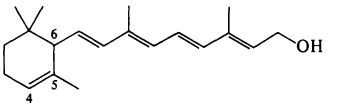
4.2.3. Derivatives of retinoic acid named as carboxylic acid derivatives following Rule C-4.6 or Rule C-403 [15]. For example (*9*) is ethyl retinoate and (*10*) is 1-*O*-retinoyl-β-D-glucopyranuronic acid.

4.3. *Changes in the Hydrogenation Level*

Retinoids that differ in hydrogenation level from the corresponding stereoparents defined by Rule Ret-2 are named by use of the prefixes 'hydro' and 'dehydro' together with locants specifying the carbon atoms at which hydrogen atoms have been added or removed. These prefixes are nondetachable, and, if both occur in one name, are cited in the order dehydro before hydro (multiplying prefixes do not affect the order); see Rule Car-6 [13]. Examples:



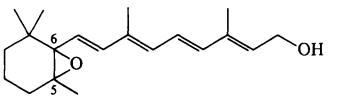
3,4-Didehydroretinol (also known as dehydroretinol[4] or vitamin A_2)



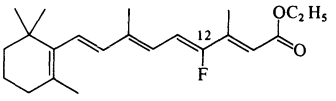
4,5-Didehydro-5,6-dihydroretinol (also known as α-vitamin A)

4.4. *Substituted Retinoids*

Substituted derivatives of retinoids are named by the use of prefixes according to the rules of general organic chemical nomenclature, see Rule C-0.1 [15]. The use of suffixes is not possible since the stereoparents defined by Rule Ret-2 include a suffix concerned with the function at C-15. Examples:



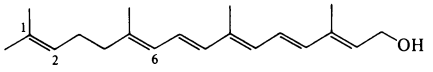
5,6-Epoxy-5,6-dihydroretinol (also known as hepaxanthin)



Ethyl 12-fluororetinoate

4.5. *Seco Retinoids*

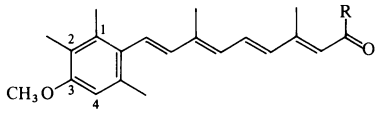
Fission of the ring, with addition of one or more hydrogen atoms at each terminal group thus created, is indicated by the prefix 'seco', the original retinoid numbering being retained (see Rule F-4.7 [14]). Example:



1,6-Seco-1,2-didehydroretinol (also known as γ-vitamin A)

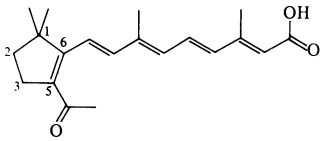
4.6. *Nor Retinoids*

Elimination of a CH_3, CH_2, CH or C group from a retinoid is indicated by the prefix 'nor', which is preceded by the locant of the carbon atom removed. When alternatives are possible, the locant selected is the highest possible, and the basic numbering of the retinoid is retained. The prefix is nondetachable (see F-4.2, F-4.4 [14]). Note that this recommendation follows rules F-4.2 and F-4.4, rather than the carotenoid recommendation (Car-5.1 [13]), which specifies the lowest possible locant. We propose that Car-5.1 should be changed to conform to the general practice when the carotenoid recommendations are next revised. Examples:



R = NHC_2H_5 *N*-Ethyl-3-methoxy-2-methyl-17-nor-1,2,3,4-tetradehydroretinamide (also known as motretinide[2])

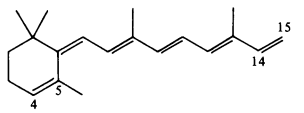
R = OC_2H_5 Ethyl 3-methoxy-2-methyl-17-nor-1,2,3,4-tetradehydroretionate (also known as etretinate[2])



5-Acetyl-4,18-dinor-retinoic acid

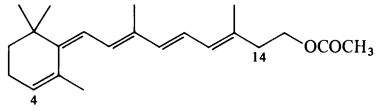
4.7. Retro *Retinoids*

The prefix '*retro*' (printed in italics) and a pair of locants indicate a shift by one position of the conjugated polyene system between the positions indicated by the locants. The first locant indicates the carbon atom that has lost a proton and the second the carbon atom that has gained one. This prefix is nondetachable (see Rule Car-9 [13]). Examples:



4,5-Didehydro-15,5-*retro*-deoxyretinol (also known as anhydro vitamin A)

Note. This semisystematic name is preferred over 14,15-didehydro-4,14-*retro*-deoxyretinol as it has the lower set of locants, see A-2.2, C-13.11 [15].



4,14-*retro*-Retinyl acetate

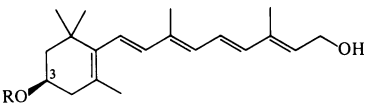
4.8. *Other Modifications*

Other modifications may be indicated by the appropriate prefix. For example; cyclo (see Rule F-4.1 [14]); homo (see Rule F-4.5 [14]); hetero atoms (see Rule F-4.11 [12], Rule B-4 and Rule C-0.6 [14]); and additional rings (see Rule 2S Appendix [17]).

Ret-5. STEREOCHEMISTRY

5.1. *Chiral Groups*

The absolute configuration at chiral centres is designated by use of the *RS* convention, the symbols being placed, with the corresponding locants, before the retinoid name (see Rule E-4.9 [18]). Examples:

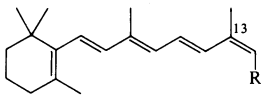


R = H (3*R*)-3-Hydroxyretinol

R = $COCH_3$ (3*R*)-3-Acetoxyretinol

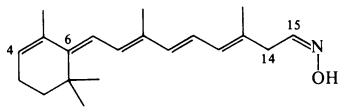
5.2. *Double Bonds*

The stereoparent name defined by Rule Ret-2 implies that the polyene chain has the *trans* configuration about all double bonds unless the contrary is indicated. Following the designation of absolute configuration (if any), *cis* double bonds are indicated. The stereochemical prefixes *E* or *Z* (see Rule E-2 [18]) may be used, and should always be used where *cis* or *trans* might be ambiguous. However it should be noted that substitution may result in a change from *E* to *Z* or *vice versa* even though there is no change in configuration of the stereoparent polyene chain. Hence it is recommended that the stereochemistry of all double bonds should be cited when this system is used. For example compound (*9*) is ethyl (*all-E*)-retinoate. Replacement of the hydrogen at C-12 by fluorine gives the compound used to illustrate rule Ret-4.4 which may be described as ethyl (7*E*,9*E*,11*Z*,13*E*)-12-fluororetinoate. Examples:



R = CH_2OH 13-*cis*-Retinol or (7*E*,9*E*,11*E*,13*Z*)-retinol (also known as neovitamin A)

R = CO_2H 13-*cis*-Retinoic acid or (7*E*,9*E*,11*E*,13*Z*)-retinoic acid (also known as isotretinoin[2])



(6*E*,8*E*,10*E*,12*E*,15*Z*)-4,14-*retro*-Retinal oxime

Note that if it is necessary to indicate the stereochemistry of the 6(7)-double bond of a *retro*-retinoid this should be stated so that, for example, the compound given with Ret-4.7 is (6*Z*,8*E*,10*E*,12*E*)-4,14-*retro*-retinyl acetate.

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APPENDIX

Some Related Terpenoids Containing less than Twenty Carbon Atoms

The term carotenoid is usually restricted to terpenoids that retain the two central methyl groups of the parent C_{40} compound. However the definitions in Rule Car-1 and Rule Car-10 [13] permit an extension of the apo nomenclature to include retinoids (e.g. retinal would be 15-apo-β-caroten-15-al) and a range of smaller molecules. Many of these compounds exhibit plant hormone action or are important essential oil components. The list of trivial names in this Appendix is given for convenience but is not intended as official recognition of these names.

Trivial name	Semisystematic name
(+)-Abscisic acid	(7E,9*Z*)-(6*S*)-6-hydroxy-3-oxo-11-apo-ε-caroten-11-oic acid
(−)-Actinidiolide	(5*R*)-3,4-didehydro-5,8-dihydro-8-apo-β-caroten-8,5-olide
Actinidol	5,8-epoxy-3,4-didehydro-5,8-dihydro-9-apo-β-caroten-9-ol
Blumenol A	(6*S*,9*R*)-6,9-hydroxy-9-apo-ε-caroten-3-one
Blumenol B	(6*S*,9*R*)-6,9-dihydroxy-7,8-dihydro-9-apo-ε-caroten-3-one
Blumenol C	9-hydroxy-7,8-dihydro-9-apo-ε-caroten-3-one
β-Cyclocitral	7-apo-β-caroten-7-al
β-Cyclogeraniol	7-apo-β-caroten-7-ol
β-Cyclogeranic acid	7-apo-β-carotin-7-oic acid
Damascenone	(8*E*)-3,4,8,9-tetradehydro-7,8-dihydro-9-apo-β-caroten-7-one
Digiprolactone	see Loliolide
Grasshopper ketone	(3*S*,5*R*,6*R*)-3,5-dihydroxy-6,7-didehydro-5,6-dihydro-9-apo-β-caroten-9-one
(+)-α-Ionone	(6*R*)-9-apo-ε-caroten-9-one
β-Ionone	9-apo-β-caroten-9-one
(−)-γ-Ionone	(6*S*)-9-apo-γ-caroten-9-one
ψ-Ionone	9-apo-ψ-caroten-9-one
(+)-*cis*-α-Irone	(2*R*,6*S*)-2-methyl-9-apo-ε-caroten-9-one
(−)-*trans*-α-Irone	(2*R*,6*R*)-2-methyl-9-apo-ε-caroten-9-one
(+)-β-Irone	(2*R*)-2-methyl-9-apo-β-caroten-9-one
β-Ionylideneacetaldehyde	11-apo-β-caroten-11-al
β-Ionylideneacetic acid	11-apo-β-caroten-11-oic acid
β-Ionylideneethanol	11-apo-β-caroten-11-ol

(continuation)

Trivial name	Semisystematic name
(−)-Loliolide	(3*S*,5*R*)-3-hydroxy-5,8-dihydro-8-apo-β-caroten-8,5-olide
Latia luciferin	(9*E*)-7,8-dihydro-10-apo-β-caroten-10-yl formate
(−)-Phaseic acid	(7*E*,9*Z*)-(1*R*,5*R*,6*S*)-5,16-epoxy-6-hydroxy-3-oxo-5,6-dihydro-11-apo-β-caroten-11-oic acid
Pseudoionone	see ψ-Ionone
Safranal	3,4-didehydro-7-apo-β-caroten-7-al
(−)-Theaspirone	(6*S*,9*S*)-6,9-epoxy-7,8-dihydro-9-apo-ε-caroten-3-one
Trisporic acid B	(1*S*)-4,13-dioxo-11,12-dihydro-13-apo-β-caroten-16-oic acid
Trisporic acid C	(1*S*,13*R*)-13-hydroxy-4-oxo-11,12-dihydro-13-apo-β-caroten-16-oic acid
Trisporol B	(1*S*)-16-hydroxy-11,12-dihydro-13-apo-β-carotene-4,13-dione
Trisporol C	(1*S*,13*R*)-13,16-dihydroxy-11,12-dihydro-13-apo-β-caroten-4-one
Trisporone	(1*S*)-11,16-dihydroxy-11-apo-β-caroten-4-one
Vomifoliol	see Blumenol A
(−)-Xanthoxin	(7*E*,9*Z*)-(3*S*,5*R*,6*S*)-5,6-epoxy-3-hydroxy-5,6-dihydro-11-apo-β-caroten-11-al