Structure / Nomenclature Guide

A Guide to the Graphic Representation and Nomenclature of Chemical Formulae in the European Pharmacopoeia

European Pharmacopoeia

European Directorate for the Quality of Medicines & HealthCare

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NOMENCLATURE AND GRAPHIC REPRESENTATION OF CHEMICAL FORMULAE

CONTENTS

PREAMBLE

The guide on nomenclature and graphic representation of chemical formulae has been prepared to reply to a number of questions from the European Pharmacopoeia Commission and users of the Ph. Eur.

I. CHEMICAL NAME OR GRAPHIC REPRESENTATION?

In principle, a chemical structure or name alone can be used to define a chemical compound. However, the Ph. Eur. uses both to facilitate checking and to remove ambiguities. Each system has its advantages and disadvantages, which are summarised below.

1. STRUCTURES

Advantages: molecules are immediately recognisable and their structures are easily compared.

Limits: there is a risk of some inaccuracy with any representation of a chemical structure because it involves drawing a molecule with a 3-dimensional structure in 2 dimensions; bond angles and lengths are not necessarily depicted accurately.

2. NAMES

Advantages: stereochemistry is specified directly with no need to interpret the structure.

Limits: nomenclature rules are very complex, numerous and difficult to master; at present, there are no rules that can be used to determine which name is officially preferable.

II. SCOPE OF THE GUIDE

Four types of compounds in the Ph. Eur. involve structures and nomenclature: parent substances, reagents, chemical reference substances and impurities.

1. PARENT SUBSTANCES

These are drawn by the scientific officers responsible for structure/nomenclature; they are then validated and named by the expert in structures and nomenclature (S/N expert).

2. REAGENTS

Trivial names are given to reagents because they are shorter and do not contain special characters (prime symbols, Greek symbols), which complicate electronic searches when the USB and online versions are used. When a reagent corresponds to an impurity, its trivial name is placed in parentheses after the name of the impurity. In the test for related substances, the name of an impurity corresponding to a reagent may be specified in parentheses to establish a link to the prescribed limit.

3. CHEMICAL REFERENCE SUBSTANCES

These substances are named systematically, being given:

– either the name of the substance if it is the subject of a monograph (first priority), for example, *ketobemidone CRS*;

– or the name of an impurity of a given substance, in which case only the active part is mentioned (neither the salt nor the solvate), for example, *ketobemidone impurity A CRS* rather than *ketobemidone hydrochloride impurity A CRS*.

4. IMPURITIES

Impurities are represented in a similar manner to the parent substance to make it clear that they are structurally analogous. They are drawn by the scientific officers responsible for structure/nomenclature. They are then validated and named by the S/N expert, usually during the Pharmeuropa stage. Contrary to previous practice, impurities are no longer grouped. For editorial reasons, it has been decided not to indicate salts, counter-ions and solvates for impurities, unlike for parent substances.

III. STRUCTURE OF THE GUIDE

This guide consists of 5 sections that deal with distinct aspects of chemical structures and nomenclature.

1. SECTION A

This section describes the rules for drawing structures based on WHO recommendations but omits rules that are not applied by the Ph. Eur.

2. SECTION B

This section is intended for use as a reference to reply to most of the questions on structures and nomenclature raised during public enquiries or during sessions of the Commission, by setting out in print the editorial rules observed by the S/N expert.

3. SECTION C

This section refers to the main structural classes of compounds whose structures are clearly analogous.

4. SECTION D

This section describes the nomenclature rules used as references by the Ph. Eur. to name substances.

5. SECTION E

This section consists of Frequently Asked Questions (FAQ) concerning structures and nomenclature and the standard answers to these questions.

SECTION A - General rules for graphic representation

INTRODUCTORY NOTE

It is important for chemical names and graphic representations in the Ph. Eur. to be defined as precisely and as unambiguously as possible. It is possible to draw many different 2-dimensional representations of a given molecule, all of which are entirely correct from a chemical standpoint. For editorial reasons and for consistency, conventions should be applied so that 2 persons, working independently, will draw a chemical structure in the same way. In this context, the Ph. Eur. follows the recommendations of the World Health Organization on the drawing of structures [1]. If there is any ambiguity in the structure, the systematic name established in accordance with the rules of the International Union of Pure and Applied Chemistry [3,13] is used to remove this ambiguity. This guide is intended to lay out the rules followed by the Ph. Eur. and to illustrate them with examples from the monographs.

A-1. GRAPHIC CONVENTIONS

I. ORIENTATION OF THE STRUCTURES

Wherever possible, structures are drawn horizontally rather than vertically. They are orientated so that the atom with the highest number is on the left with the numbering of atoms decreasing from left to right [1].

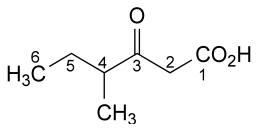


Figure A-1-1

II. NUMBERING OF RINGS

Rings are numbered according to the rules of chemical nomenclature. Wherever possible, rings are numbered in a clockwise direction [1].

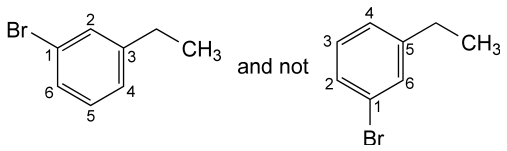


Figure A-1-2

III. REPRESENTATION OF CHEMICAL GROUPS

1. General rule

Links between atoms are represented by dashes. Structures are shown in full. Polyatomic groups are drawn so that the atoms are shown as close as possible to the dashes representing the links [1].

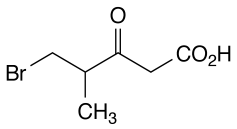


Figure A-1-3

2. Condensed form

Certain groups, however, are shown in condensed form [1].

Table A-1-1. Groups shown in condensed form

—CH_3	methyl	—CHO	formyl
—CN	cyano	—NC	isocyano
—CO_2H	carboxy	—CO_2^-	carboxylate
—OH	hydroxy	—OCH_3	methoxy
—NH_2	amino	—NO_2	nitro
—SO_3H	sulfo	—SO_3^-	sulfonate
—N_3	azido		

It is strongly recommended to avoid using the following symbols for condensed representations, except in the case of polypeptides [1]:

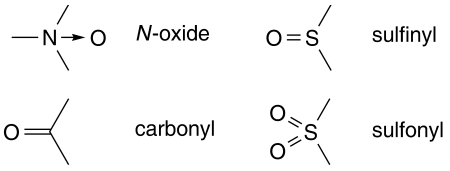
—Me —Et —Pr —Ph

Figure A-1-4

3. Expanded form

A choice has been made on how to depict characteristic groups. The various classes of compounds are assembled from such groups [1].

Table A-1-2. Groups represented in expanded form



IV. SPECIAL CASE OF N-OXIDES

At present there is no consensus on how to depict *N*-oxides, and the following representations co-exist:

– A simple N-O bond with a + charge on the N and a – charge on the O. However, this representation needlessly complicates structures and names.

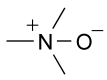


Figure A-1-5

– An arrow pointing from the N to the O.

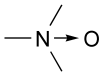


Figure A-1-6

– An N=O double bond.

Figure A-1-7

It has been decided to represent *N*-oxides in the Ph. Eur. with an arrow until a consensus is reached. Comments have already been made on this matter (see section E).

A-2. ACYCLIC STRUCTURES

I. REPRESENTATION OF COVALENT BONDS

1. Convention for different types of bonds

In acyclic structures, a single bond is shown as a single dash, a double bond as a double dash, and a triple bond by a triple dash [1].

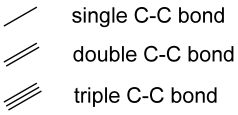


Figure A-2-1

2. Distinctive characteristic of double bonds

In linear structures, double bonds are shown as centered between the two atoms (in cyclic structures, double bonds are shown inside the ring; see section A-3).

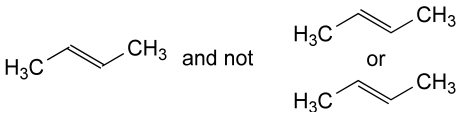


Figure A-2-2

3. Distinctive characteristic of triple bonds

Triple bonds impose a fixed linear structure. The two remaining bonds of the carbon atoms are drawn along the axis of the triple bond.

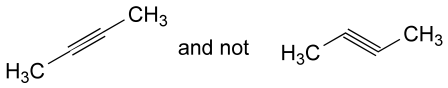


Figure A-2-3

II. REPRESENTATION OF CARBON CHAINS

1. Angular representation

In the Ph. Eur., the entire carbon chain is shown. The chains are drawn as lines at angles to one another since this representation makes it easier to describe the centres of asymmetry. The carbon and hydrogen atoms are intentionally omitted from the chain to simplify the appearance of the main structure; the chain is simply represented by a series of links at an angle to one another. Only the terminal groups are shown. Groups on the left-hand end of the formula are inverted, with the hydrogen atoms to the left of the carbon atom. [1].

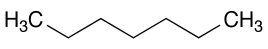


Figure A-2-4

2. Chains containing repeated groups

Parentheses

Parentheses are not usually used to show that several identical groups are linked to the same atom or to a group linked to the principal chain [1] except for certain very complicated structures and for the definition of substituent groups in the case of grouped impurities (see section B-1).

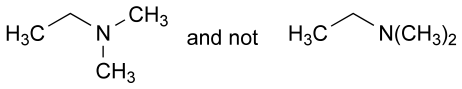


Figure A-2-5

Square brackets

Square brackets are used to indicate the repetition of a large number of identical groups. If one of these groups terminates the chain or bears a heteroatom, it is shown outside the square brackets [1].

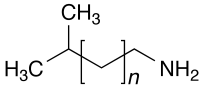


Figure A-2-6

In the Ph. Eur., square brackets are used only when a structure is too large to fit into a single column or when substituent groups are defined (see section B-1). It is aesthetically preferable, but not obligatory, to use square brackets rather than fold back the structure in the plane. The repeating unit may be linear (Figure A-2-7) or branched (Figure A-2-8).

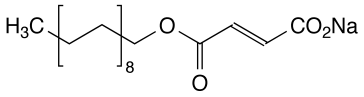


Figure A-2-7. – *Sodium stearyl fumarate (1567)*

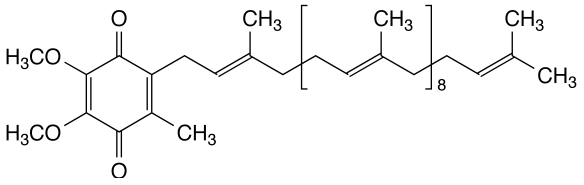


Figure A-2-8. – *Ubidecarenone (1578)*

III. STEREOCHEMICAL INDICATIONS

Only the carbon atoms and hydrogen atoms at the end of a chain are shown systematically. However, hydrogen atoms can be shown if this is necessary to specify the stereochemistry.

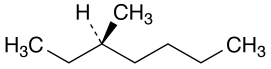


Figure A-2-9

It should be noted that stereochemical indications are given in the Ph. Eur. wherever necessary (see section A-7). Whenever there is ambiguity, this should be clarified.

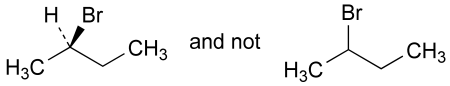


Figure A-2-10

To specify the stereochemistry of a centre of asymmetry, a single bond can be replaced by a broken line (bond projecting behind the plane of the paper) or a filled wedge (bond projecting in front of that plane) [1]. The rules for stereochemical representation are described in more detail in section A-7 of this guide.

Double bonds and triple bonds cannot be represented spatially; if such a bond is attached to a centre of asymmetry, it is shown in the plane of the paper and the single bonds are depicted to show the stereochemistry [1].

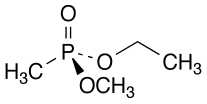


Figure A-2-11

A-3. CYCLIC STRUCTURES

I. BASIC GEOMETRIC FORMS

1. Monocyclic systems

Rings are shown as regular polygons when they consist of up to 8 carbon atoms [8].

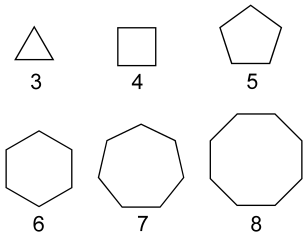


Figure A-3-1

Rings with more than 8 vertices are often shown with re-entrant angles. The Chemical Abstract Service (CAS) recommends that they should be drawn like amalgamated rings with 5, 6 or 7 vertices [8].

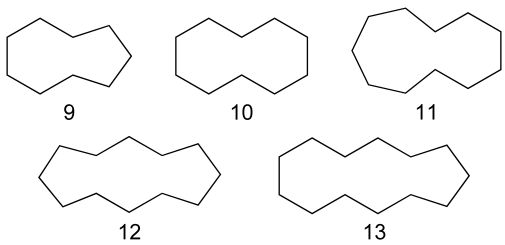


Figure A-3-2

2. Polycyclic systems

Wherever possible, the regularity of the polygons is maintained in the drawing of fused cyclic compounds [8].

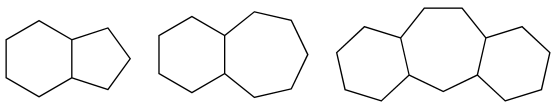


Figure A-3-3

However, in fused polycyclic systems the polygons may often be distorted in order to maintain the symmetry of the structure [8].

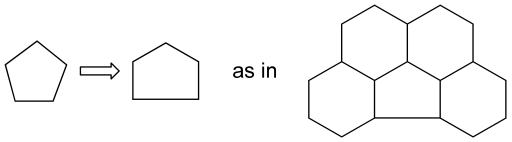


Figure A-3-4

II. HETEROCYCLES

Rings are shown in full. The symbols of the carbon atoms that form the ring are not shown. The hydrogen atoms attached to them are not represented unless they are needed to show stereochemistry. Heteroatoms are shown with all the hydrogen atoms attached to them but without linking dashes [1].

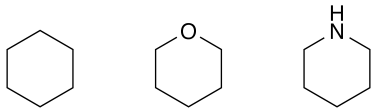


Figure A-3-5

Trivial names exist for heterocycles that can be used to establish a nomenclature.

III. UNSATURATED SYSTEMS

In aromatic systems, all the double bonds are shown [1]. The Ph. Eur. does not use a circle to depict delocalised electrons.

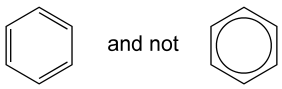


Figure A-3-6

1. Monocyclic systems

Double bonds are shown inside the ring rather than being centred between 2 carbon atoms.

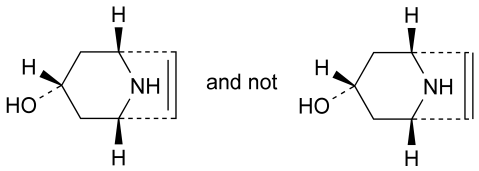


Figure A-3-7

In monocyclic compounds, by convention, double bonds should be arranged to have the lowest possible numbering [1].

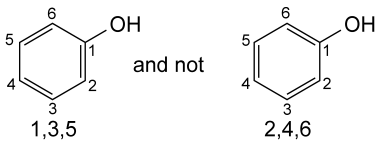


Figure A-3-8

2. Polycyclic systems

In fused polycyclic systems a double bond should form the fusion bond nearest to the right-hand side, where there is a choice possible [8].

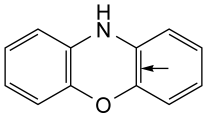


Figure A-3-9

IV. SUBSTITUENTS AND INDICATED HYDROGENS

Substituents and indicated hydrogens are normally placed outside monocyclic or polycyclic systems if the configuration of the rings permits this (sufficient space).

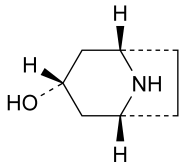


Figure A-3-10

In the case of steroids, terpenes and alkaloids and of crowded structures, substituents and indicated hydrogens attached at bridgeheads can be displayed inside the rings of polycyclic structures [8].

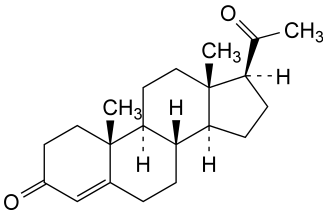


Figure A-3-11

A-4. IONIC STRUCTURES

I. GENERAL RULES OF PRESENTATION

1. Order of appearance of ions

The following rules apply to the drawings of parent substances but do not apply either to impurities, which are drawn as conjugate acids and bases, or to quaternary ammonium salts, which are drawn without showing the counter-ion.

In most cases, the ion can be represented in condensed form (see section A-1); the structure is then drawn as if it were not an ion. This is done in particular for salts of alcoholates, carboxylates, and phosphoric and sulfuric esters

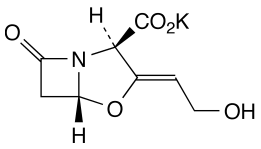


Figure A-4-1. – *Potassium clavulanate (1140)*

In general, in ionic structures, the cationic part is placed on the left and the anionic part on the right [1]. Cations and anions are not separated by a comma or a dot.

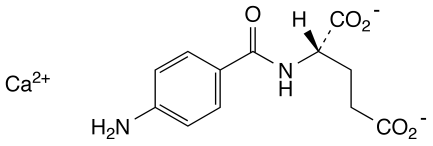


Figure A-4-2

2. Symbolising the charge

Ionic charges are not encircled and are shown as superscripts on the right of the charged atom.

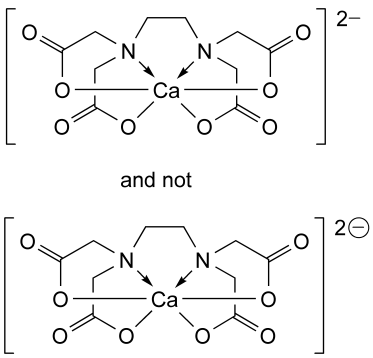


Figure A-4-3

Multiple charges are indicated by writing *n*+ or *n*– and not by writing the + or – symbol *n* times [1].

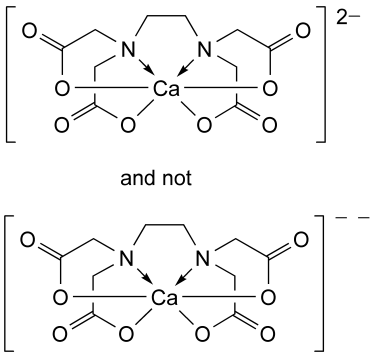


Figure A-4-4

3. Placing the charge on the molecule

A terminal charge is shown as a superscript on the right of the group concerned, unless the order of atomic symbols in the group is reversed, in which case the charge is shown as a superscript on the left.

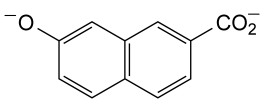


Figure A-4-5

In structures where the positions of the charges cannot be indicated precisely, the structure is put in square brackets, with the overall charge placed outside them as a superscript on the right.

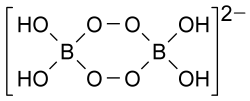


Figure A-4-6

In a horizontal acyclic chain, if there is no space for a superscript on the right of the atom concerned, the charge can be shown immediately above that atom.

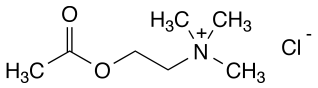


Figure A-4-7. – *Acetylcholine chloride (1485)*

When a ring is involved, the charge is usually placed outside the ring, unless it is impossible to place the charge without ambiguity [1].

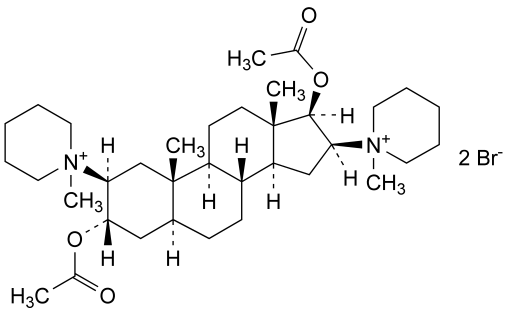
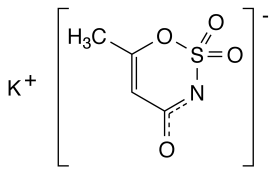


Figure A-4-8. – *Pancuronium bromide (0681)*

II. DELOCALISED CHARGE

In structures with a delocalised charge, the structure is put in square brackets, with the charge sign outside them as a superscript on the right [1].



Figures A-4-9. – *Acesulfame potassium (1282)*

III. SUBSTANCES WITH SEVERAL GROUPS THAT CAN FORM SALTS

1. Case of several acid groups forming different salts

When substances contain several acid groups to which the various cations cannot easily be attributed, ionic forms may be used [1].

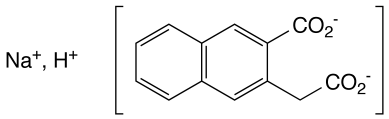


Figure A-4-10

2. Zwitterions

For zwitterions, the + and – charges are drawn and placed according to the rules described above [1], provided that these charges are indispensable.

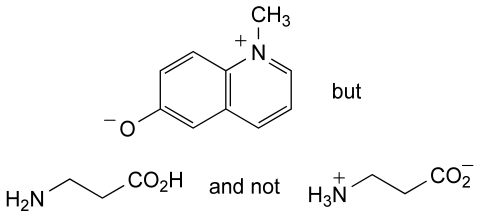


Figure A-4-11

IV. SOLVATE SALTS

The Ph. Eur. does not follow the IUPAC recommendation to use a dot to symbolise solvates of inorganic compounds. It uses a comma for both organic and inorganic compounds. It should be noted that for molecular formulae, the Ph. Eur. does not put spaces between the comma, the number of molecules of water and the molecular formula for water. However, these are separated by spaces in structural formulae.

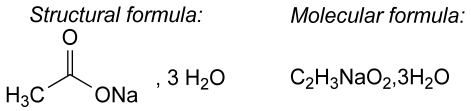


Figure A-4-12

V. METAL SALTS

1. Inorganic salts

Metal salts (for example, $KMnO_4$), like inorganic acids (for example, $HClO_4$), are shown without charges or bonds. Structural formulae are not given for these substances in the monographs since the molecular formula is considered to be sufficient, except in the case of co-ordination compounds for which the stereochemistry of the complexes must be specified (see section A-6). If metal salts of inorganic acids include several metals, the symbols for the metals are shown in alphabetical order (for example, K_2NaPO_4). In salts of inorganic acids, the metal precedes the hydrogen (for example, NaH_2PO_4) [1]. Molecules of water of crystallisation or of substances of solvation follow the formula of the salt, from which they are separated by a comma, without a preceding or following space (for example, $H_3PO_4,5H_2O$ or $Na_2SO_4,{}^3/_2H_2O$).

2. Organic salts

In the metal salts of organic acids and the metal compounds of alcohols, phenols (and their sulfur, selenium and tellurium analogues), amines and amides, the metal symbol usually replaces the acid hydrogen [1].

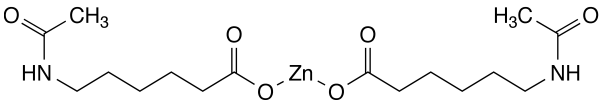


Figure A-4-13. – *Zinc acexamate (1279)*

VI. AMINE SALTS

Amine salts are shown with the structure of amine on the left (as if it were in the ammonium form) and, after a comma, the formula of the inorganic acid on the right [1].

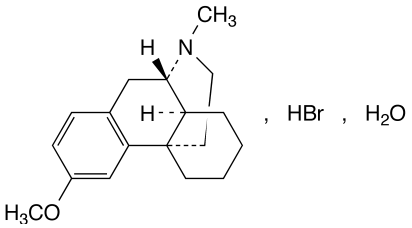


Figure A-4-15. – *Dextromethorphane hydrobromide (0020)*

Quaternary ammonium salts and other compounds with a positive charge on a heteroatom (P, As, Sb, O, S, Se, Te) are shown in ionic form (with + and – charges), the 2 ions being separated by a space [1].

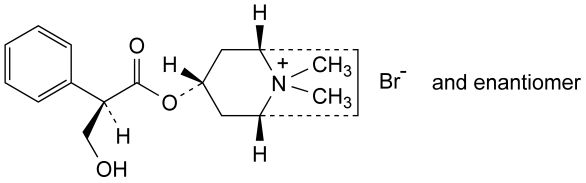


Figure A-4-16. – *Methylatropine bromide (0511)*

A-5. ISOTOPICALLY MODIFIED COMPOUNDS

In most monographs on radiopharmaceutical substances in the Ph. Eur. a structural or molecular formula is not given. However, it may be necessary to indicate them in certain monographs.

In an isotopically modified compound, the isotope used is indicated by its mass number placed as a superscript on the left of the symbol of the element concerned. Deuterium and tritium are written ^{2}H and ^{3}H, respectively [1].

The carbon atom in a ring or a simplified angular-chain representation is explicitly designated when its mass number is shown [1].

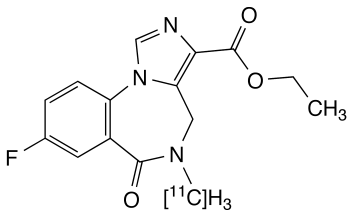


Figure A-5-1. – *Flumazenil (N-[^{11}C]methyl) injection (1917)*

To indicate isotopic labelling (partial replacement of the atom by the nuclide shown), atomic symbols in formulae should be in square brackets [1].

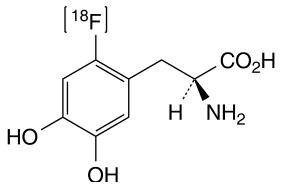


Figure A-5-2. – *Fluorodopa (^{18}F) (prepared by electrophilic substitution) injection (1918)*

When atomic symbols and formulae are drawn without square brackets, the compounds are assumed to be isotopically substituted, i.e., the atom concerned is completely replaced by the nuclide shown [1]. This is not usually the case in the monographs.

A-6. COORDINATION COMPOUNDS

I. NON-CYCLIC LINEAR STRUCTURES

According to current usage [2], for example, *Sodium nitroprusside (0565)*: $Na_2[Fe(CN)_5(NO)],2H_2O$, a noncyclic structure is constructed in the following order:

– the symbol of the central atom placed on the left,

– ionic ligands with cations first and then anions,

– neutral ligands.

Polyatomic ligands are placed in parentheses, with the atom linked to the central atom on the left, for example, $Na_2[Fe(CN)_5(NO)],2H_2O$. If several identical ligands are attached to the central atom, their number is indicated as a subscript to the right. In each class of ligand, the symbol of the linking atom is shown, followed by the other atoms in alphabetical order. The complete formula of the coordination entity (neutral group or complex ion) is placed in square brackets [1]. No spaces should be left between representations of ionic species within the formula of a coordination compound.

If the charge of the coordination entity needs to be specified, it is placed outside the square bracket as a right superscript [1]. The individual charges usually carried by the central atoms and the ligands are not normally shown; they may, however, be shown in structural formulae when it is difficult to show all the coordination links [1].

II. CYCLIC STRUCTURES

The rings follow the conventions for cyclic compounds (see section A-3). Where possible, the metal atom is placed in the centre of the group. Square brackets are placed round every coordination entity containing one or more rings, even if the charge is zero [1].

'Sandwich' structures are shown with the rings connected to the central atom by a line starting from inside the cycle and passing through one side [1]. Benzene rings and condensed benzene systems in 'sandwich' compounds are drawn with alternating single and double bonds. Pentagonal and heptagonal rings are shown with a circle inside [1].

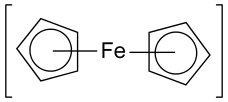
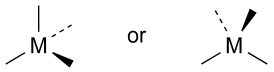


Figure A-6-1

III. STEREOCHEMISTRY

The stereochemistry of mononuclear complexes is expressed by means of special descriptors formed from an abbreviation for the central atom geometry and the coordination number [1].

Table A-6-1

Polyhedral symbol	Representation
T-4	
SP-4	
TBPY-5	
SPY-5	
OC-6	
PBPY-7	

Coordination bonds of the shared-electron-pair type are shown as arrows directed towards the central atom (see Figure A-6-2); these arrows do not project in front of or behind the paper and must be drawn in the plane of the paper. The other co-ordination entities are orientated accordingly.

1. *T*-4: tetrahedral complexes

They are described by the chirality symbols (*R*) and (*S*); they are shown in the same way as stereogenic carbon atoms, following the same convention [1].

2. *SP*-4: square planar complex

The 4 co-ordination links are shown in the plane of the paper [1].

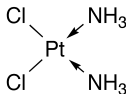


Figure A-6-2. – *Cisplatin (0599)*

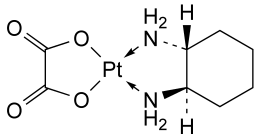


Figure A-6-3. – *Oxaliplatin (2017)*

3. *TBPY*-5: trigonal bipyramidal complex

The reference axis is shown in the plane of the paper; of the 3 other, equatorial ligands, 1 is assumed to be also in the plane of the paper, 1 in front of it and the other behind it [1].

4. *SPY*-5: square pyramidal complex

The reference axis with its lone coordinating atom is shown in the plane of the paper and 4 co-ordination links are assumed to be in a plane perpendicular to the reference axis, 2 in front of and 2 behind the plane of the paper [1].

5. *OC*-6: octahedral complex

Two coordination links are shown as the axis in the plane of the paper and 4 are assumed to be in a plane perpendicular to the reference axis, 2 in front of and 2 behind the plane of the paper [1].

6. *PBPY*-7: pentagonal bipyramidal complex

Two coordination links are shown as the axis in the plane of the paper and the 5 other coordination links are shown as their projection onto the plane perpendicular to this axis: 1 in the plane of the paper, 2 in front of it and 2 behind it [1].

A-7. STEREOCHEMISTRY

I. GENERAL ASPECTS

The rules are applied when permitted by the spatial constraints of the molecule. Stereochemistry is the branch of chemistry concerned with the 3-dimensional arrangement of atoms in molecules, and stereoisomers are isomers with no differences in connectivity or bond multiplicity, but whose atomic spatial arrangements differ. As already mentioned, a broken line denotes a bond projecting behind the plane of the paper and a filled wedge denotes one projecting in front of that plane. A line of normal thickness denotes a bond lying in the plane of the paper [1]. Hydrogen is represented by its symbol 'H' whenever a configuration has to be shown [1].

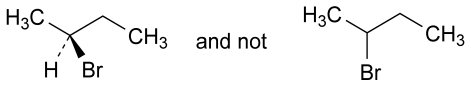


Figure A-7-1

II. GEOMETRIC ISOMERISM

1. (*EZ*) isomerism

General rules for representation

Compounds containing carbon-carbon double bonds are represented as lines at an angle to each other; the representations of (*EZ*) isomers show that the (*Z*) configuration produces a bend in the chain whereas the (*E*) configuration does not.

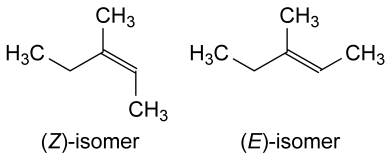


Figure A-7-2

It should be noted that the hydrogens attached to the 2 carbon atoms forming the double bond are omitted [1] in the case of (*EZ*) isomerism.

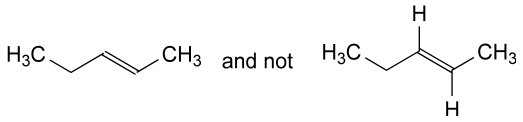


Figure A-7-3

(EZ) isomerism of imines/oximes

The same convention is used for the isomers of imines/oximes and compounds containing several double bonds [1].

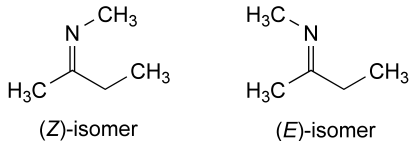


Figure A-7-4

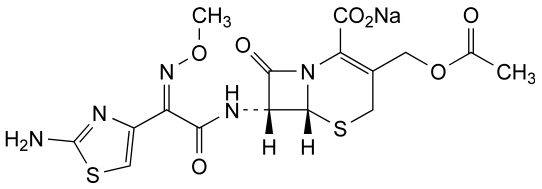


Figure A-7-5. – *Cefotaxime sodium (0989)*

How to represent a mixture of (E) and (Z) isomers of a compound

To describe a mixture of (*Z*) and (*E*) isomers of a compound, the (*E*) isomer is shown and the legend 'and (*Z*)-isomer' is added to the right of the structure. This type of representation does not necessarily mean that the 2 isomers are present in the same quantities.

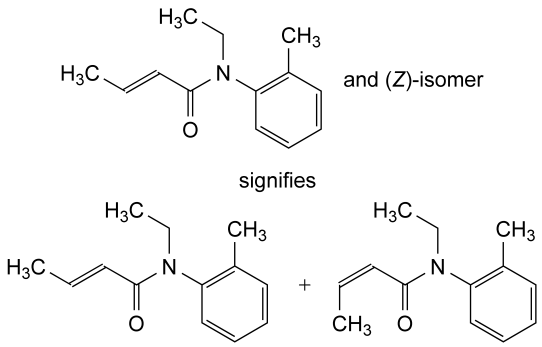


Figure A-7-6. – *Crotamiton (1194)*

How to represent the stereochemistry of a double bond when it is undefined

In certain cases, the stereochemistry of a double bond may be unknown, i.e. the group of experts does not know whether the impurity consists of the (*E*) isomer or the (*Z*) isomer or both. This lack of knowledge is represented by convention by drawing the double bond so that it is aligned with 1 of the 2 C-C bonds next to it (see Figure A-7-7).

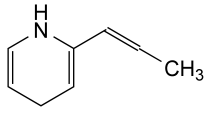


Figure A-7-7

The information conveyed by this representation is considerably different from that conveyed by the representation of a mixture of both isomers (Figure A-7-8).

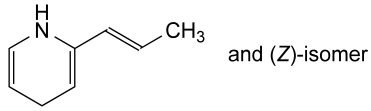


Figure A-7-8

Comments have already been made on this subject (see section E).

Summary of modes of representation for (EZ) isomerism

See Table A-7-1.

2. *cis-trans* Ring isomerism

cis-trans Ring chirality is defined for a molecule with a plane of symmetry as the existence of *cis* and *trans* isomerism according to the arrangement of substituents on a ring with respect to the plane of this ring. *N*-oxides of cyclic amines, present as oxidation impurities in the monographs on certain cyclic amines, display this type of isomerism.

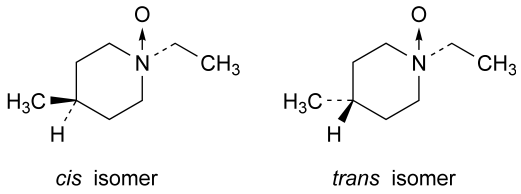
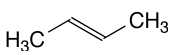
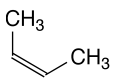
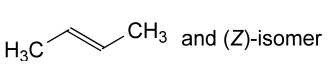
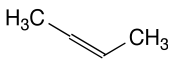


Figure A-7-9

How to represent a mixture of cis-trans ring isomers of a compound

To describe a mixture of *cis-trans* ring isomers of a compound, the *cis* isomer is shown and the legend 'and *trans* isomer' is added to the right of the structure. This type of representation does not necessarily mean that the 2 isomers are present in the same quantities.

Table A-7-1. – Representations of (*EZ*) isomerism

Representation	Isomer present	Type of stereochemistry
	(*E*)	defined
	(*Z*)	defined
	(*E*) + (*Z*)	defined
	(*E*) or (*Z*) or (*E*) + (*Z*)	undefined

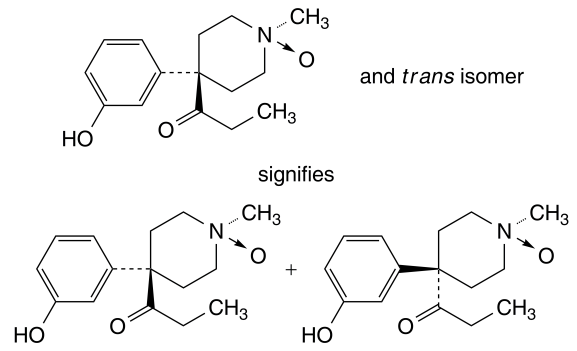


Figure A-7-10. – Impurity A of *Ketobemidone hydrochloride (1746)*

Comments have already been made on this subject (see section E).

III. COMPOUNDS WITH ONE CENTRE OF ASYMMETRY

Rules for representation of enantiomers

An enantiomer is one of a pair of molecular entities that are mirror images of each other and non-superposable [4]. Diastereoisomerism is defined as stereoisomerism other than enantiomerism. Diastereoisomers are stereoisomers not related as mirror images [4].

Enantiomerism of sulfoxides

Sulfoxides show enantiomerism. Questions are frequently asked about this (see section E).

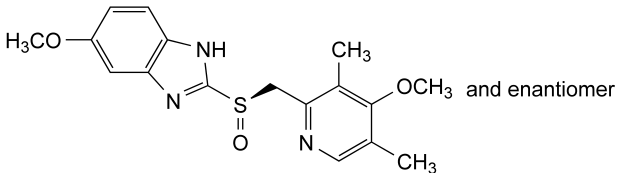


Figure A-7-12. – *Omeprazole (0942)*

Undefined chirality

If the chirality of the centre of asymmetry is unknown or not specified, the bonds adjoining atoms or groups to the chiral atom are shown as lines of 'normal' thickness and an asterisk identifies this chiral centre [1]. Monosaccharides and macrolides are exceptions for which a bond with an unknown orientation is symbolised by a wavy line.

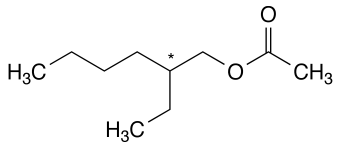


Figure A-7-13.

How to represent a mixture of enantiomers of a compound

To describe a mixture of 2 enantiomers of a compound, the (*R*)-isomer is shown and the phrase 'and enantiomer' is added to the right of the structure. This type of representation does not necessarily mean that the 2 isomers are present in the same quantities. If they are present in the same quantities, the term used is racemate or racemic mixture.

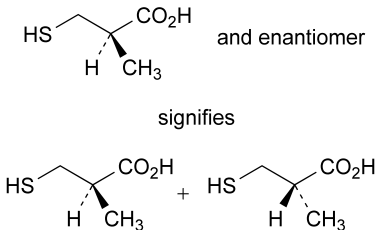


Figure A-7-14

Summary of modes of representation of (RS) isomerism

See Table A-7-2.

IV. COMPOUNDS WITH SEVERAL CENTRES OF ASYMMETRY

In compounds containing several centres of asymmetry, the same conventions apply to each of these centres [1].

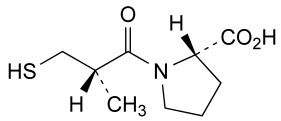


Figure A-7-15. – *Captopril (1079)*

This is also the case for the representation of *cis-trans* isomerism relative to a ring.

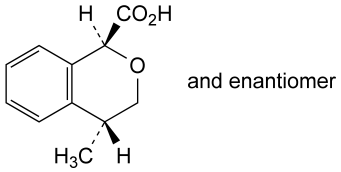


Figure A-7-16

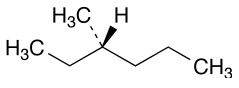
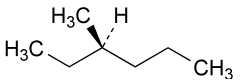
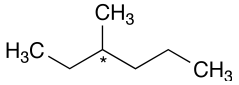
1. Epimers

General rules of presentation

Epimers are diastereoisomers that have the opposite configuration at only 1 of 2 or more tetrahedral stereogenic centres present in the respective molecular entities [4]. If a compound has 2 centres of asymmetry, there are 4 different stereoisomers. Two epimers of this compound have the same configuration at one centre of asymmetry and a different configuration at the other.

Mixtures of 2 epimers

Table A-7-2. – Representations of (*RS*) isomerism

Representation	Isomer present	Type of stereochemistry
	(*R*)	defined
	(*S*)	defined
 and enantiomer	(*R*) + (*S*)	defined
	(*R*) or (*S*) or (*R*) + (*S*)	undefined

To define a mixture of 2 epimers of a compound containing at least 2 asymmetrical carbons, draw the (*R*) isomer with respect to the centre of asymmetry of interest marked with an asterisk and add the legend 'and epimer at C*' to the right of the structure [1].

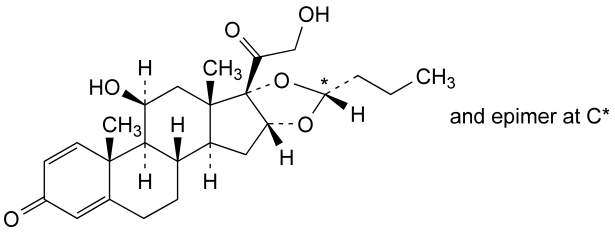


Figure A-7-17. – *Budesonide (1075)*

If the 2 centres of asymmetry are, for example, a carbon atom and a nitrogen atom, draw the (*R*) isomer with respect to the centre of asymmetry of interest, without an asterisk, and add the legend 'and epimer at C' or 'and epimer at N' to the right of the structure.

2. Anomers

General rules of presentation

A special case of epimerism is that of anomerism of sugars. Anomers are defined as diastereoisomers of glycosides, hemiacetals or related cyclic forms of sugars, or related molecules differing in configuration only at C-1 of an aldose, C-2 of a 2-ketose, etc [4].

Mixtures of 2 anomers

To define a mixture of 2 anomers of a compound containing at least 2 centres of asymmetry, draw the (*R*) isomer with respect to the centre of asymmetry of interest marked with an asterisk and add the legend 'and anomer at C*' to the right of the structure [1].

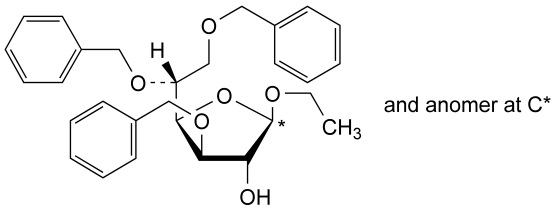


Figure A-7-18. – *Tribenoside (1740)*

3. Mixtures of more than 2 stereoisomers

To define a mixture of more than 2 isomers of a compound containing at least 2 centres of asymmetry, proceed in 2 steps:

– first, identify the centres of asymmetry that permutate together and isolate 2 groups of enantiomers;

– second, isolate the marginal centre of asymmetry (C*), which is the centre used to establish the link between the 2 groups of enantiomers.

Next, show the (*R*) isomer at C* and add the legend 'and epimer at C*', which defines both of the above mentioned groups. The legend 'and their enantiomers' is also added, which means that for the 2 defined epimers there are 2 isomers, giving a total of 4 isomers. This construction can be broken down for greater clarity (see Figure A-7-19).

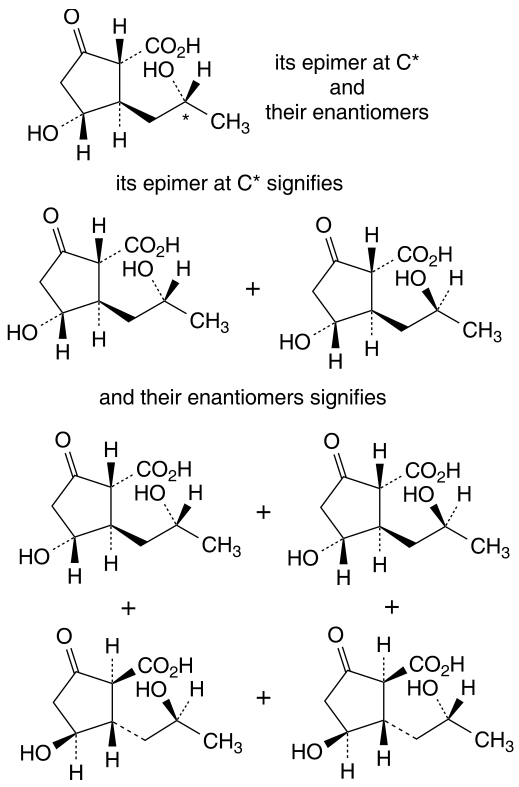


Figure A-7-19

The Ph. Eur. includes monographs on such mixtures (Figures A-7-20 and A-7-21).

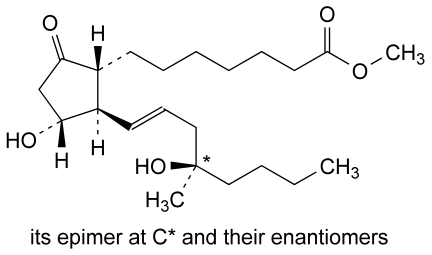


Figure A-7-20. – *Misoprostol (1731)*

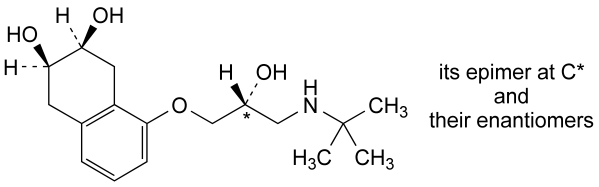


Figure A-7-21. – *Nadolol (1789)*

V. STEREODESCRIPTORS IN SYSTEMATIC NOMENCLATURE

(*R*) and (*S*)

These symbols (proposed by Cahn, Ingold and Prelog) indicate the absolute configuration around 4-coordinate (quadriligant) and 6-coordinate (sexiligant) stereogenic centres.

(*r*) and (*s*)

The stereodescriptors *r* and *s* (lower-case italics) are used instead of *R* and *S* to designate the stereochemistry of a carbon atom that is stereogenic because it has 4 different substituents (2 of which differ only in terms of stereochemistry), but which is part of a structure that is non-chiral due to a plane of symmetry passing through this carbon atom.

SECTION B - Graphic rules specific to the Ph. Eur.

INTRODUCTORY NOTE

The general rules described in section A of this guide are not always strictly followed and sometimes have been adapted to the scientific and editorial requirements of the Ph. Eur. In addition, unlike the WHO, the Ph. Eur. describes impurities (Impurities section of monographs, sometimes called the 'transparency list'). As the structures are not available in the INN database, they are drawn and named entirely by the Ph. Eur. for its users.

- Large structures in particular must be drawn so that they fit into one of the 2 columns on a page (i.e. maximum 8.5 cm wide).
- For reasons of clarity, impurities are not drawn independently of the parent substance that is the subject of the monograph. The impurities are in fact related to this substance since most of the time they are its degradation products. The drawings of the impurities are derived from the structure of the parent substance, modified as necessary.

This section describes the specific rules to be applied to achieve these 2 objectives.

B-1. GROUPING OF STRUCTURES

I. GENERAL PRINCIPLES

The Ph. Eur. groups structures together when the parent substance is defined as a mixture of compounds with similar structure.

The Ph. Eur. no longer groups impurities. Grouped impurities in existing monographs will be ungrouped when the concerned monographs are revised or corrected.

Grouping of structures involves:

- identifying the constant part among the molecules, so as to define the largest common denominator, and drawing this generic structure;
- identifying the parts that vary between structures and defining the relevant substituent groups to be specified in the name.

Section A of this guide describes the general rules for drawing generic structures; an additional objective is to show the structures of the impurities in a manner that makes it clear that they are related. The section below describes the recommendations to be followed for substituent groups.

II. THE VARIOUS SUBSTITUENT GROUPS

The Ph. Eur. groups structures together by means of substituent groups, whose nature depends on the group to be described and on the bond in particular:

- *monovalent groups* are attached to the generic structure by a single bond;
- *divalent groups* are attached to the generic structure by 2 single bonds or 1 double bond;
- *repetition units* describe a repeating unit (in the carbon chain of the generic structure).

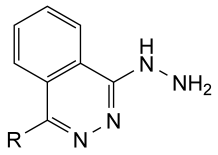
It is possible to describe 1 or more substituent groups of a given type for the same structure. The editorial recommendations to be followed are described below for each type. Substituent groups must be as small as possible and generic structures must be as large as possible. For certain structures shown together, the various types of substituent groups may be combined on the same structure. These should therefore be considered independently and the rules described below for each type should be followed.

1. Monovalent groups

A monovalent group is an atom or group of atoms linked to a generic structure by only 1 single bond. Several cases can be described depending on whether 1, 2 or more groups have to be defined; there are specific editorial rules for each case.

Case No. 1 – 1 monovalent group

When there is a single monovalent group it is designated R. The group is specified just before the name of each entity.

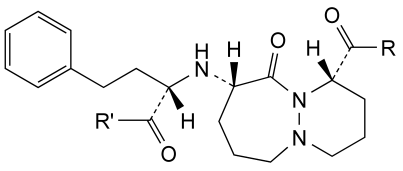


A. R = NH_2
C. R = H

Figure B-1-1

Case No. 2 – 2 monovalent groups

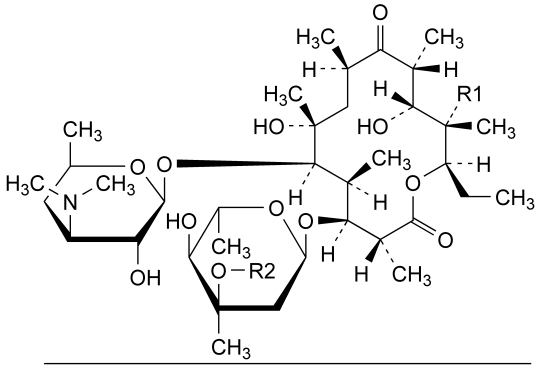
When there are exactly 2 monovalent groups, they are usually designated R and R′.



A. R = $C(CH_3)_3$, R' = C_2H_5
B. R = R' = H
C. R = R' = C_2H_5

Figure B-1-2

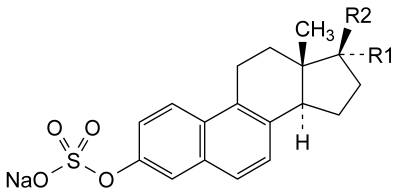
They may, however, be designated R1 and R2, in particular in crowded structures where the prime symbol might not be noticed. It should be noted that the number given to the substituent group should not be written as a subscript to avoid confusion with the subscripts in chemical groups (indicating the number of times that the atom is present in a polyatomic group).



Erythromycin	Mol. Formula	M_r	R1	R2
A	$C_{37}H_{67}NO_{13}$	734	OH	CH_3
B	$C_{37}H_{67}NO_{12}$	718	H	CH_3
C	$C_{36}H_{65}NO_{13}$	720	OH	H

Figure B-1-3

The case of R + R′ = O or R1 + R2 = O is a special case that makes it possible to show a ketone or an imine with its homologous alkane/amine/alcohol, as illustrated below.



E : R1 = OH , R2 = H
F : R1 = H , R2 = OH
H : R1 + R2 = O

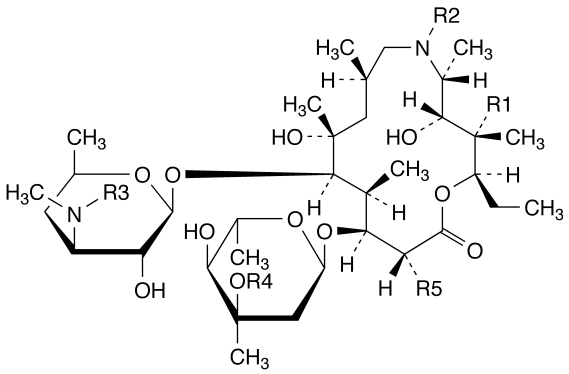
Figure B-1-4

It is also possible to do this using divalent groups (see case No. 4).

Comments have already been received on this subject (see section E).

Case No. 3 – more than 2 monovalent groups

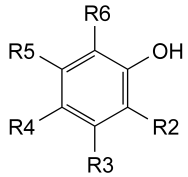
When more than 2 monovalent groups are identified, they are designated R1, R2, R3... R*n*.



A : R1 = OH, R_2 = H, R_3 = R_4 = R_5 = CH_3
B : R1 = H , R_2 = R_3 = R_4 = R_5 = CH_3
C : R1 = OH, R2 = R3 = R5 = CH_3, R4 = H
D : R1 = OH, R2 = R3 = R4 = CH_3, R5 = CH_2OH
F : R1 = OH, R2 = R4 = R5 = CH_3, R3 = CHO
G : R1 = OH, R2 = R4 = R5 = CH_3, R3 = SO_2-C_6H_4-CH_3
I : R1 = OH, R2 = R4 = R5 = CH_3, R3 = H

Figure B-1-5

In principle, the number assigned to a substituent group is independent of its position in the structure, except in the simple case where the groups are attached to an aromatic ring, and where systematic numbering applies. It should be noted that R1 is almost always missing (the principal group is in position 1). Other intermediary substituent groups may also be missing (R3 may be missing without affecting the numbering of R2, R4, R5 and R6).



A : R2 = R3 = R4 = R5 = R6 = H
B : R2 = CH_3, R3 = R4 = R5 = R6 = H
C : R2 = R3 = R5 = R6 = H, R4 = CH_3
D : R2 = R6 = CH_3, R3 = R4 = R5 = H

Figure B-1-6

Comments have already been received on this subject (see section E).

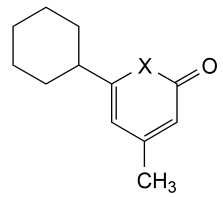
2. Divalent groups

A divalent group is an atom or group of atoms able to form 2 single bonds or 1 double bond with the generic structure.

Case No. 4 – 1 divalent group

When a single divalent group is identified, it is designated X. X may form:

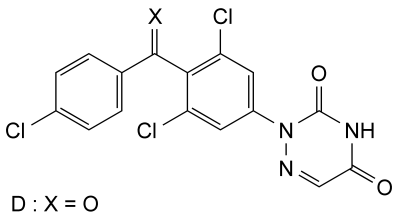
– 2 single bonds to 2 different atoms:



B : X = O
C : X = NH

Figure B-1-7

– 1 double bond to a single atom:



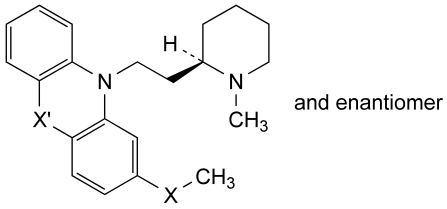
D : X = O
F : X = H_2

Figure B-1-8

X = H_2 is a special case which enables a ketone or an imine to be grouped with its homologous alkane, as shown above.

Case No. 5 – 2 divalent groups

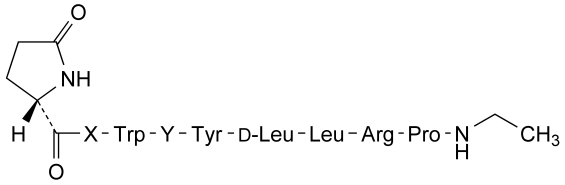
In chemical compounds, when 2 divalent groups are identified, they are designated X and X′.



A : X = X' = SO_2
B : X = SO, X' = S
C : X = S, X' = SO
D : X = SO, X' = SO
E : X = SO_2, X' = S

Figure B-1-9

In peptides, when 2 divalent groups are identified, they are designated X and Y.

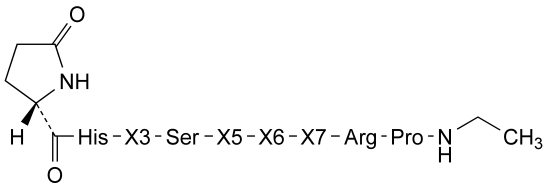


A. X = L-His, Y = D-Ser
B. X = D-His, Y = L-Ser
F. X = D-His, Y = D-Ser

Figure B-1-10

Case No. 6 – More than 2 divalent groups

When more than 2 divalent groups are identified, they are designated X1, X2, X3... X*n*. This is very rare for chemical products but is very frequent for peptides.



C. X3 = L-Trp, X5 = L-Tyr, X6 = X7 = L-Leu
E. X3 = D-Trp, X5 = L-Tyr, X6 = D-Leu, X7 = L-Leu
G. X3 = L-Trp, X5 = D-Tyr, X6 = D-Leu, X7 = L-Leu
H. X3 = L-Trp, X5 = L-Tyr, X6 = X7 = D-Leu

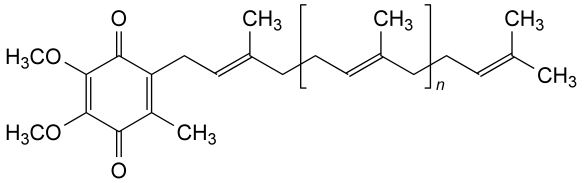
Figure B-1-11

For peptides/proteins, the number assigned to the substituent group corresponds to the number assigned to the amino acid that it replaces in the current structure. This makes it easier to check the name.

3. Repetition units

As is the case for polymers, repeating units can be shown in square brackets, where *n* is the number of times the unit is repeated.

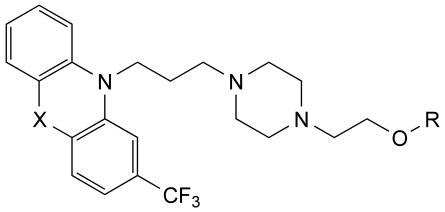
Case No. 7 – 1 repetition unit



B : *n* = 5
C : *n* = 6
D : *n* = 7

Figure B-1-12

It is not absolutely necessary to do this and a sustituent group R that is itself defined as a polymer can also be introduced.



A : X = SO, R = H
C : X = S, R = CO-$[CH_2]_5$-CH_3
D : X = S, R = CO-$[CH_2]_6$-CH_3
E : X = S, R = CO-$[CH_2]_7$-CH_3

Figure B-1-13

Case No. 8 – 2 repetition units

When 2 repetition units are defined, they are designated *n* and *m*.

Case No. 9 – More than 2 repetition units

When more than 2 repetition units are defined, they are designated *x, y, z, n, m*.

Summary of the various substituent groups

See Table B-1-1.

III. SPECIAL RECOMMENDATIONS FOR PEPTIDES/PROTEINS

For peptides, when several substituent groups have to be described for an impurity and some are from the L series and others are from the D series, the relevant series should be specified clearly.

Table B-1-1. – Representations of substituent groups

Representation	Type of group	Area of application
R	monovalent	1 monovalent group defined
R and R′ or R1 and R2	monovalent	2 monovalent groups defined
R1, R2, R3... R*n*	monovalent	more than 2 monovalent groups defined
X	divalent	1 divalent group defined
X and X′ or X and Y	divalent	2 divalent groups defined
X1, X2, X3... X*n*	divalent	more than 2 divalent groups defined
n	repetition	1 repetition group defined
n and *m*	repetition	2 repetition groups defined
x, y, z, n, m	repetition	more than 2 repetition groups defined

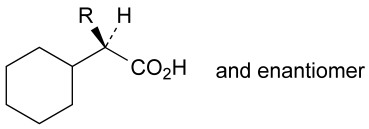
When an amino acid is replaced, there are 2 equivalent nomenclature systems that can be used. For example, if the 2nd amino acid of leuprorelin is replaced by D-leucine, the impurity is called [D-Leu^2]leuprorelin or [2-D-leucine]leuprorelin, with the first name being preferred.

IV. SPECIAL RECOMMENDATIONS FOR TERTIARY AND QUATERNARY AMMONIUM SALTS

A tertiary ammonium salt and its quaternary homologue are never grouped by means of a substituent group R linked to the nitrogen atom (which would take the value R = H for the tertiary amine). It is not the amine salts that are described but rather the corresponding bases.

V. GROUPING AND ISOMERISM

A chiral impurity and a non-chiral impurity can be grouped by defining substituent groups attached to the centre of asymmetry.



A. R = OH
B. R = H

Figure B-1-14

Comments are often made on this subject (see section E).

In the case of a grouped structure defined as a mixture of (*E*) and (*Z*) isomers, see impurities B and C in the monograph on *Halothane (0393)*.

B-2. MIXTURES OF COMPOUNDS

I. GENERAL PRINCIPLES

Some parent substances or impurities are defined as mixtures of 2 or more compounds with different structures or relatively similar structures. For more than 50 years, WHO policy on INNs [9] has been not to assign an INN to mixtures of substances except in the case of natural products (in particular, antibiotics produced by fermentation) for which the substances meet the 3 following criteria:

– they have very similar structures;
– they have comparable activities;
– they cannot be separated during their isolation.

Other substances for pharmaceutical use are described as mixtures; this is the case for most excipients (polymers in particular). Sometimes these have been assigned an INN but usually it is not used, with the trivial name or chemical name being favoured [9]. Finally, there are rare cases of associations between several compounds in fixed proportions that have been assigned an INN [9].

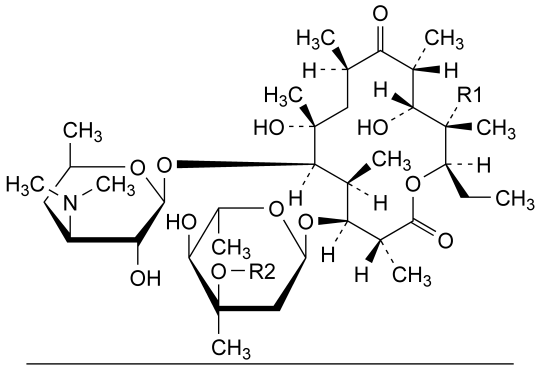
There are various editorial rules according to the case:

– mixtures of structures that can be grouped using radicals;
– mixtures of structures that cannot be grouped using radicals;
– mixtures of 2 structural groups;
– mixtures of structures that are not shown in the Ph. Eur.

II. MIXTURES OF STRUCTURES THAT CAN BE GROUPED

When the parent substance is a mixture of grouped structures, the generic structure is shown along with a table that provides information on the various compounds making up the mixture. These compounds are usually classified in order of decreasing content in the mixture; the main compound is therefore mentioned first.

Macrolide antibiotics that are produced by isolation from fermentation media of *Streptomyces* strains are usually described as mixtures of compounds with structures that can be grouped using radicals.



Erythromycin	Mol. Formula	M_r	R1	R2
A	$C_{37}H_{67}NO_{13}$	734	OH	CH_3
B	$C_{37}H_{67}NO_{12}$	718	H	CH_3
C	$C_{36}H_{65}NO_{13}$	720	OH	H

Figure B-2-1. – *Erythromycin (0179)*

III. MIXTURES OF STRUCTURES THAT CANNOT BE GROUPED

In this case, the 2 structures are shown with a + sign between them. When the molecular ratio between the 2 entities is not defined, see the content of each compound given under Definition.

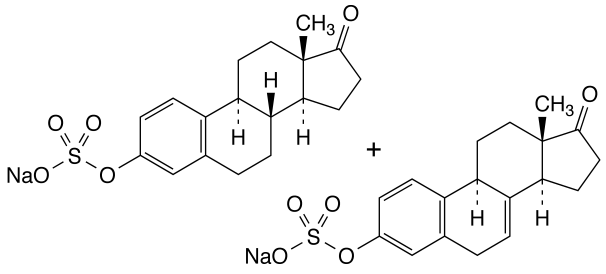


Figure B-2-2. – *Conjugated estrogens (1512)*

VI. MIXTURES OF STRUCTURES THAT ARE NOT SHOWN IN THE PH. EUR.

In certain cases, a monograph may describe a mixture of structures (in particular for heparins and for oils). In this case, a decision is taken with the administrator responsible for the monograph not to show the structures since information that is relevant to the user cannot be presented because of the complexity of the mixture. The mixture is described under Definition as a mixture of compound A and compound B, and the approximate proportions are indicated.

B-3. ORGANIC AND INORGANIC SALTS

I. GENERAL PROVISIONS

1. Salts of a parent substance

Representation of salts

Both organic and inorganic salts are represented in the Ph. Eur. with a comma separating the parent structure from the acid or base with which it forms the salt.

Molecular ratio

The molecular ratio is usually shown just before the acid or base used to form the salt. If no molecular ratio is shown, the ratio is 1:1 by default. If this ratio is unknown or variable, an '*x*' is indicated before the molecular formula of the acid or base used to form the salt; this is done especially for products of fermentation and peptides/proteins.

2. Salts of an impurity

Impurities are not shown in the Ph. Eur. as salts, even if the subject of the monograph is a parent substance in the form of a salt. Primary, secondary and tertiary ammonium salts are represented as the corresponding uncharged base. For quaternary ammonium salts, the cation is shown but not the counter-ion.

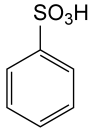
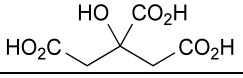
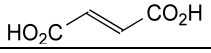
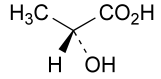
II. INORGANIC SALTS

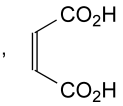
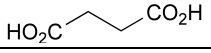
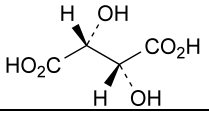
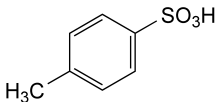
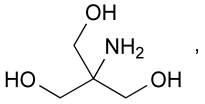
The salts of inorganic acids are shown by placing the molecular formula of the acid after a comma. Various types of inorganic acid salts are described in the Ph. Eur. (see Table B-3-1).

III. ORGANIC SALTS

For reasons of consistency in the Ph. Eur., the salts of organic acids or bases are always drawn in the same manner. However, rotation of the organic acid or base in question is tolerated to save space.

Table B-3-1. – Principal salts of the Ph. Eur.

Salt	Representation
Acetate	, H_3C-CO_2H
Besilate	, 
Hydrobromide	, HBr
Hydrochloride	, HCl
Citrate	, 
Fumarate	, 
Lactate	,  and enantiomer

Salt	Representation
Maleate	, 
Mesilate	, H_3C-SO_3H
Nitrate	, HNO_3
Oxalate	, HO_2C-CO_2H
Phosphate	, H_3PO_4
Succinate	, 
Sulfate	, H_2SO_4
Tartrate	, 
Tosilate	, 
Trometamol	 ,

IV. ORDER OF PRESENTATION OF THE COMPONENTS OF THE SALT

For organic salts, the general principle for representing ions is followed: the structures are presented in the same order as when the salt has been formed so that the cation is placed first followed by the anion, which give the 2 following cases. When an organic acid is used to form the salt, it is placed last:

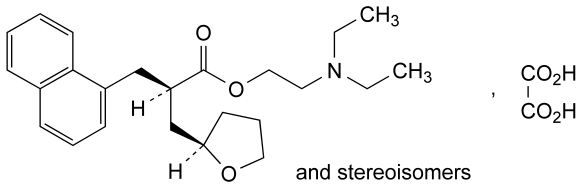


Figure B-3-7. – *Naftidrofuryl hydrogen oxalate (1594)*

When an organic base is used to form the salt, it is placed first:

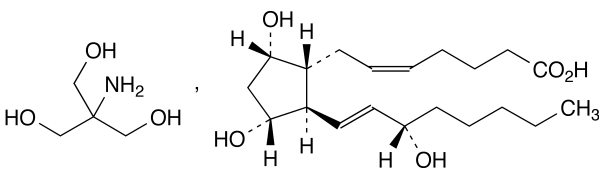


Figure B-3-8. – *Dinoprost trometamol (1312)*

B-4. TITLES OF MONOGRAPHS

I. INTERNATIONAL NONPROPRIETARY NAMES (INN)

INNs are assigned by the WHO, and when they are recommended they must be used as the titles of monographs. If objections to an INN have been formulated, its use is more delicate and a decision must be taken with the producer on a case-by-case basis.

1. Gender of INNs in French

A rule has been established to determine the gender of INNs in French: names ending in '-one' or '-ine' are feminine and all the others are masculine [7].

2. Salts and esters

When an INN is assigned to a particular salt or ester (for example, levothyroxine sodium), the name of the acid or the base, or that of another other salt or ester, may be chosen as a modified INN (INNM) (for example, levothyroxine) derived from the recommended INN [7].

3. INNs for substituents and groups

INNs have been devised for groups whose names are too long or too awkward to use (for example, mesilate for methanesulfonate) [9]. These INNs make it possible to avoid using stereodescriptors or italics in the titles, thus simplifying the labelling of pharmaceutical substances (for example, derbumine salt is preferable to *tert*-butylamine salt).

4. Substances not covered by INNs

In principle, INNs are not assigned to:

- mixtures of substances (with certain exceptions);
- substances that are not completely characterised (with certain exceptions);
- herbal substances;
- homoeopathic preparations;
- substances that have been in medical use for a long time under a well-established name (for example, alkaloids) or under a trivial chemical name.

Exceptions to the above are the following:

- mixtures isolated from biological sources (mainly antibiotics);
- products obtained via a chemical reaction yielding a mixture of homologous compounds (in particular synthetic polymers).

II. MODIFIED INNS

WHO guidance now exists on the elaboration of modified INNs (namely salts and esters, which are of particular interest to the Ph. Eur.) from recommended INNs [21].

III. EXCIPIENTS

The derivation of Ph. Eur. monograph titles for excipients is much less homogeneous than for active substances since it may be based on the chemical name, the trivial name or (less frequently) the INN, where it exists. Usage is the main selection criterion [7].

SECTION C - Main structural classes

The Ph. Eur. has monographs on many substances belonging to the main structural classes. Structures of substances belonging to the same class are drawn in a manner that shows their structural analogy. This makes it easier to compare visually the structures of

substances in the same class and also to identify the common parts as well as the specific parts of the structures. In addition, this approach has the editorial advantage of ensuring that structures are depicted uniformly and consistently in all the monographs.

Despite the existence of general rules described in section A of this guide, it may be difficult to apply them to certain structural classes, in particular those for which there are special rules for systematic numbering, for stereochemistry or for nomenclature.

Some of the main structural classes for substances in the Ph. Eur. are listed below, for information:

- amino acids;
- monosaccharides and their derivatives;
- derivatives of purine and pyrimidine bases;
- steroids;
- terpenoids;
- prostanoids;
- alkaloids;
- antibiotics;
- peptides and proteins;
- polymers.

SECTION D - Nomenclature and application of IUPAC rules

I - IUPAC RULES APPLIED

The chemical names used in the Ph. Eur. are based on the rules of the International Union of Pure and Applied Chemistry (IUPAC) published in 'A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations, 1993)' [14] and on the nomenclature rules for carbohydrates elaborated by a IUPAC and IUBMB joint commission 'Nomenclature of carbohydrates' [15].

II - CHANGES TO IUPAC RULES

Proposed changes to IUPAC rules on specific topics have been published in *Pure & Appl. Chem.* These can be downloaded free of charge from the official IUPAC website [19]. Caution should be exercised when consulting websites that display these proposed changes mixed imprudently with the formally adopted rules (especially site [20]). The Ph. Eur. does not follow these recommendations adopted after 1993.

III - PREFERRED IUPAC NAME

For a given compound, there often are several names that are acceptable by IUPAC rules. A guide to selecting a 'preferred name' was under preparation by IUPAC and was expected to be available for enquiry in 2006. Nevertheless, the Ph. Eur. will not follow these recommendations until the document is formally adopted. For now, there are no plans to use this document for a systematic revision of the names in already published monographs.

IV - NAME SOFTWARE BY ACD/Labs

The Ph. Eur. has been using Name software produced by ACD/Labs (Advanced Chemistry Development [17]) to elaborate the names in its texts since Pharmeuropa 18.1. This software uses the same IUPAC nomenclature rules that are used by the Ph. Eur. [14,15]. The software can also be set up to operate using IUPAC 1979 rules [13]. However, IUPAC recommendations published after 1993 are not applied in the software.

SECTION E - Frequently Asked Questions (FAQ)

Questions on structures and names are often received by the Ph. Eur. after monographs are published for enquiry in Pharmeuropa. The most frequently asked questions are shown below. For more detailed answers see the corresponding section of this guide.

Your question/comment	**Answer in paragraph**
When are S/N corrections introduced into monographs?	I
How to report an error in a structure	II
How to report an error in a name	III
How to report a discrepancy between a structure and its name	IV
Why does the name indicate *r/s* instead of *R/S*?	V
What does R + R′ = O mean?	VI
Where is the R3 radical?	VII
Why is a nonchiral impurity grouped with a chiral impurity?	VII
The bond angle is wrong	II-1
The bond length is wrong	II-1
The counter-ion of an impurity is missing	II-1
The salt of an impurity is missing	II-1
The *N*-oxide is not represented properly	II-1
You wish to propose an equivalent IUPAC name	III-1
‘Sulphate’ is misspelt in English	III-1

I - WHEN ARE S/N CORRECTIONS INTRODUCED INTO MONOGRAPHS?

The structure and nomenclature expert sends his corrections between the publication of a monograph in Pharmeuropa (ANP) and its adoption by the European Pharmacopoeia Commission (COM). Usually these corrections have already been introduced into the draft submitted to the Commission for adoption. Delays nevertheless may occur and in this case it is not necessary to re-send a comment that had already been made at the Pharmeuropa stage. The corrections will be introduced before the text is published in a supplement.

II - HOW TO REPORT AN ERROR IN A STRUCTURE

1 - EDITORIAL COMMENTS

It is not necessary to point out editorial errors in the representation of a structure such as bond angles, bond lengths, the absence of the counter-ion of an impurity, the absence of the salt of an impurity or the manner of representing *N*-oxides.

2 - COMMENT ON THE CONTENT

All errors in content concerning the structure must be reported. Requests for revision or comments will be processed much more easily if they are supported by licensing data or structural determination data.

III - HOW TO REPORT AN ERROR IN A NAME

1 - EDITORIAL COMMENTS

It is not necessary to submit editorial comments on the name of a structure such as proposing equivalent IUPAC names, correcting the spelling of sulfate derivatives in English, etc.

2 - COMMENT ON THE CONTENT

Any non-editorial error concerning nomenclature must be reported. Corrections are easier to implement if the requests for revision or the comments follow IUPAC numbering rules for atoms (trivial numbering should not be used).

As the Ph. Eur. does not follow IUPAC recommendations published after 1993, it is not necessary to point out that they have not been applied.

In general, any comment on nomenclature must mention the IUPAC rule that it is based on, as well as the document in which the rule was published.

IV - HOW TO REPORT A DISCREPANCY BETWEEN A STRUCTURE AND ITS NAME

1 - SUPPLEMENT

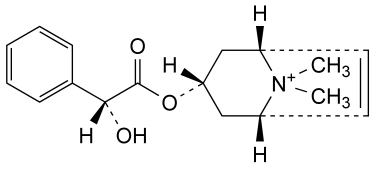
Any relevant discrepancies between a structure and its name must be pointed out for a supplement.

2 - PHARMEUROPA

Discrepancies between a structure and its name may be pointed out at the Pharmeuropa stage. It should be noted that since the expert's corrections are introduced only after the Pharmeuropa stage, it is likely that the published text will include errors.

V - WHY DOES THE NAME INDICATE *r/s* INSTEAD OF *R/S*?

The stereodescriptors *r* and *s* (lower-case italics) are used instead of *R* and *S* to designate the stereochemistry of a carbon atom that is stereogenic because it has 4 different substituents (2 of which differ only in terms of stereochemistry), but which is part of a structure that is non-chiral due to a plane of symmetry passing through this carbon atom. This case applies in particular to derivatives of atropine.

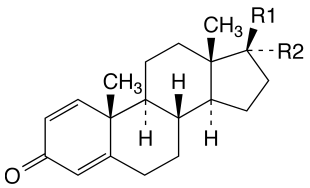


(1*R*,3*s*,5*S*)-3-[[(2*RS*)-2-hydroxy-2-phenylacetyl]-oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene

Figure FAQ-5. – Impurity A of *Homatropine methylbromide (0720)*

VI - WHAT DOES R + R′ = O MEAN?

R + R′ = O or R1 + R2 = O makes it possible to show a ketone or an imine with its homologous alkane/amine/alcohol. Obviously the bond angle is not accurately shown in this case but such a grouped presentation saves space and also shows the structural analogy between the impurities to make the transparency list easier to understand.

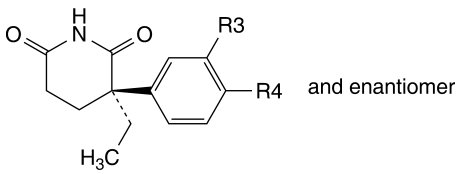


G. R1 + R2 = O
H. R1 = OH, R2 = H

Figure FAQ-6. – Impurities G to H of *Testosterone (1373)*

VII - WHERE IS THE R2 SUBSTITUENT GROUP?(1)

If the substituent groups are attached to an aromatic ring, they are numbered in accordance with systematic numbering. It should be noted that in this context R1 is almost always absent (the main functional group is in position 1). Other intermediary substituent groups may also be missing (R2 may for example be absent without modifying the numbering for R3, R4, R5 and R6).

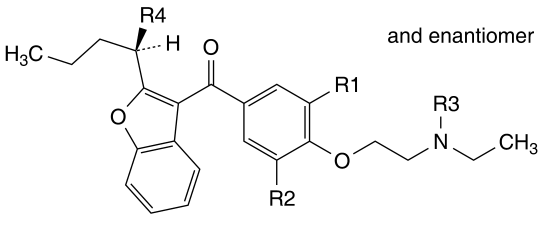


A : R3 = NH_2, R4 = H
B : R3 = NO_2, R4 = H
C : R3 = H, R4 = NO_2

Figure FAQ-7. – Impurities A to C of *Aminoglutethimide (1291)*

VIII - WHY IS A NONCHIRAL IMPURITY GROUPED WITH A CHIRAL IMPURITY?

In the Ph. Eur. a chiral impurity and a nonchiral impurity may be grouped by defining radicals attached to the centre of asymmetry. The graphic representation with the legend 'and enantiomer' is not really correct for the nonchiral impurity but the main objective of this type of grouping is to save space and also to show the structural analogy between the impurities to make the transparency list easier to understand.



A : R1 = R2 = R4 = H, R3 = C_2H_5
B : R1 = R2 = I, R3 = R4 = H
C : R1 = I, R2 = R4 = H, R3 = C_2H_5

Figure FAQ-8. – Impurities A to C of *Amiodarone hydrochloride (0803)*

(1) As impurities are progressively ungrouped, such cases are to become less frequent.

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[21] World Health Organisation. International Nonproprietary Names Modified. INN Working Document 05.167/3; 2006.