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IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN)

Nomenclature and symbols for folic acid and related compounds

(Recommendations 1986)

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These Rules are as close as possible to the published version prepared for publication by Raymond L. Blakley (St. Jude Children's Research Hospital, Memphis, Tennessee) with an expert panel whose members were C. Baugh (U.S.A.), S. J. Benkovic (U.S.A.), R. L. Blakley (convenor U.S.A.), R. B. Dunlap (U.S.A.), L. Jaenicke (Federal Republic of Germany), J. C. Rabinowitz (U.S.A.), C. Wagner (U.S.A.) and H. C. S. Wood (U.K.) [see *Eur. J. Biochem.*, 1987, **168**, 251-253; *J. Biol. Chem.*, 1987, **263**, 605-607; *Pure Appl. Chem.*, 1987, **59**, 833-836; *Biochemical Nomenclature and Related Documents*, 2nd edition, Portland Press, 1992, pages 266-268.; Copyright IUPAC and IUBMB; reproduced with the permission of IUPAC and IUBMB]. If you need to cite these rules please quote these references as their source. A [PDF \(98 kB\)](#) of the printed version is available.

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The folates are a group of heterocyclic compounds based on the 4-[(pteridin-6-ylmethyl)amino]benzoic acid skeleton conjugated with one or more L-glutamate units. The document is a revision of recommendations prepared by the IUPAC-IUB Commission on Biochemical Nomenclature in 1964. The main changes are a consequence of the much greater information that now exists about the stereochemistry of folates. Recommendations on the nomenclature of reduced compounds and substituents are included, as are proposed symbols and abbreviations.

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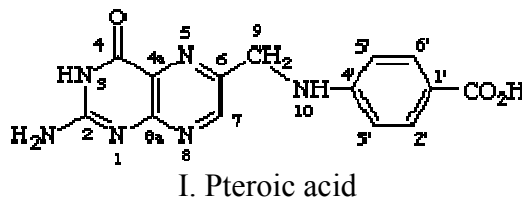
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1. INTRODUCTION

The folates are a group of heterocyclic compounds based on the 4-[(pteridin-6-ylmethyl)amino]benzoic acid skeleton (see [Formula I](#)) conjugated with one or more L-glutamate units. They were the subject of previous recommendations prepared by the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) [\[1\]](#), and the present document is a revision of the earlier one.



2. REVISED RECOMMENDATIONS

2.1. Parent compound

The compounds of this group are based on pteric acid ([Formula I](#)). The salts and the acyl group derived from the acid are named pteroates and pteroyl, respectively.

Comments

1) The systematic name of the structure shown in [formula I](#) is 4-{[(2-amino-3,4-dihydro-4-oxopteridin-6-yl)methyl]amino}benzoic acid. However, the use of 'dihydro-' in this systematic name of the parent non-reduced compound should be carefully distinguished from the use of 'dihydro-' in the names of reduced derivatives (see [section 2.6](#)).

2) 2-Aminopteridin-4(3*H*)-one also occurs in other biologically important derivatives, and may be called pterin.

2.2. Numbering

The atoms are numbered as indicated in [formula I](#).

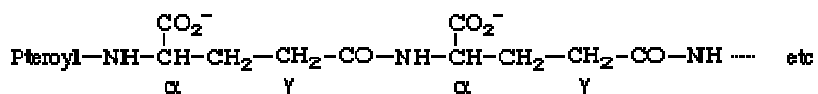
Comment

It should be noted that the nitrogen atoms numbered 5, 8 and 10 are unambiguously defined. It is therefore unnecessary to introduce the locant N into names when indicating substitution on these atoms. The carbon atoms common to the two rings are numbered 4a, 8a, so as to permit description of compounds reduced at these positions.

2.3. Glutamate conjugates

The compounds in which pteric acid is conjugated with one or more molecules of L-glutamate are named pteroylglutamate, pteroyldiglutamate, etc. (The name pteroylmonoglutamate is not used. See also [paragraph 2.4](#)) It is assumed that the second and subsequent molecules of glutamate are each linked by

amide bonds to the preceding molecule of glutamate through the γ -carboxyl of the latter, thus:



These terms may also be used in a generic sense. Thus 'pteroylhexaglutamates' may be used to designate any compounds with this basic structure, or a mixture of them, regardless of the state of reduction of the pteridine ring or one-carbon substitutions on the reduced pteridine ring. The term 'pteroylpolyglutamates' has a still broader connotation, applying to all members of the family with more than one glutamate residue.

2.4 Folate and folic acid

Folate and folic acid are the preferred synonyms for pteroylglutamate and pteroylglutamic acid, respectively.

2.5. Generic use of the term folates

The term folates may also be used in the generic sense to designate any members of the family of pteroylglutamates, or mixtures of them, having various levels of reduction of the pteridine ring, one-carbon substitutions and numbers of glutamate residues.

2.6. Reduced compounds

Reduced compounds are indicated by the prefixes 'dihydro-', 'tetrahydro-', etc., with numerals indicating the positions of the additional hydrogen atoms, if known. A tetrahydro- compound is assumed to be substituted in the 5, 6, 7 and 8 positions, and a dihydro- compound is assumed to be substituted in the 7 and 8 positions, unless otherwise indicated.

As the absolute configuration at C-6 in the natural stereoisomers of tetrahydropteroylglutamates is known, *R*, *S*, or *ambo*- should be used to designate the configuration whenever possible. (The prefix *ambo*- indicates that a mixture is present, one of whose components is *R* and the other *S* at the locus designated; it is especially useful when they are not present in equal proportions, because of the presence of other chiral centres in the molecule, such as those of glutamate residues. It is explained more fully in sections [3AA-13.2](#) and [3AA-19.2](#) of [ref. 3](#)). All of the known natural stereoisomers have the same configuration as (6*S*)-tetrahydrofolate, with the H on C-6 placed below the plane of the paper when the formula is drawn as in [formula I](#), but are variously designated *R* or *S* according to the priority rules (section E, appendix 2, of [ref. 2](#)). Examples are given in [section 2.8\(f\)](#) below. Where the configuration at C-6 is unknown in compounds bearing a hydrogen atom at this point, the symbols (+), (-) or (\pm) may be used to indicate optical activity.

2.7. Substituents

The common substituents are indicated by prefixes taken from the general Organic Nomenclature Rules [\[2\]](#) together with the locants of the positions substituted. It should be noted that the substituent prefixes mean that the substituent replaces one hydrogen atom in the parent structure in the case of formyl, methyl or formimino, or two hydrogen atoms in the case of methylene and methenyl. This must be taken into account in balancing equations that involve tetrahydrofolates. The substituents methylene (CH_2) and methenyl (CH) (see [Table 1](#)) form bridges between nitrogens 5 and 10 of reduced folates. In the case of methenyl a positive charge is associated with the $\text{N}^+=\text{CH}=\text{N}^+$ structure.

Table 1

Substituent	Symbol	Formula
Formimino*	NHCH-	HN=CH-
Formyl	HCO-	O=CH-
Methyl	CH ₃ -	CH ₃ -
Methylene	-CH ₂ -	-CH ₂ -
Methenyl*	-CH ⁺ -	-CH= as component of [$>\text{N}-\text{CH}=\text{N}^+< \leftrightarrow >\text{N}^+=\text{CH}-\text{N}<$]

* The systematic names for HN=CH- and -CH= are iminomethyl (or formimidoyl) and methyldiyne respectively; however, the names given are those that are commonly used in biochemical practice. Formimino should not be confused with formylimino, HC(O)N<.

For convenience, the prefix indicating reduction (dihydro- or tetrahydro-) is treated as being 'non-detachable' (see section C-16.1 of [ref. 2](#)), and so is placed immediately before the stem name (folate, pteroylglutamate). Other substituent prefixes (see [Table 1](#)) are placed in front of dihydro- or tetrahydro-.

2.8. Symbols and abbreviations

It is often convenient to designate compounds of this series by symbols for the sake of brevity, particularly in equations, tables and figures. The following principles are to be applied. In all cases where confusion might arise, symbols are to be defined, or the names of compounds written out in full.

- a) Folate is preferred to folic acid, and, because it is short, it should not be abbreviated.
- b) Pterate (or pteroyl or pteric acid) is indicated by the three-letter symbol Pte.
- c) The pteroylglutamates and the corresponding acids are indicated by the symbols PteGlu, PteGlu₂, PteGlu₃, etc., the subscript numerals indicating the number of glutamate units. (The symbol Glu is taken from the standard amino-acid symbols [\[3\]](#). In the folate series, Glu implies L-glutamate linked via its γ-carboxyl group as indicated in [paragraph 2.3](#) above, unless stated to the contrary.)
- d) Reduced derivatives are indicated by H₂ or H₄ in front of the main symbol with an indication of the position if necessary, e.g. H₂folate, H₄PteGlu₃. DH and TH should not be used.
- e) Substituents are indicated by symbols derived from their abbreviated formulae, as shown in [Table 1](#), prefixed by appropriate locants.
- f) H₂, H₄ and other prefixes may be used with 'folates' or with 'pteroylglutamates' when reduced or reduced-modified compounds are meant (without specifying the number of glutamate residues per molecule).

The following are some examples of natural stereoisomers:

(6 <i>S</i>)-H ₄ folate	(6 <i>S</i>)-5,6,7,8-tetrahydrofolate [(6 <i>S</i>)-5,6,7,8-tetrahydropteroylglutamate]
(6 <i>R</i>)-5,10-CH ₂ -H ₄ folate	(6 <i>R</i>)-5,10-methylenetetrahydrofolate
(6 <i>S</i>)-5-CH ₃ -H ₄ PteGlu ₃	(6 <i>S</i>)-5-methyltetrahydropteroyltriglutamate
(6 <i>R</i>)-10-HCO-H ₄ PteGlu _{<i>n</i>}	(6 <i>R</i>)-10-formyltetrahydrofolates for (6 <i>R</i>)-10-formyltetrahydropteroylpolyglutamates, if <i>n</i> = 1 is to be excluded)
(6 <i>R</i>)-5,10-CH ⁺ -H ₄ folate	(6 <i>R</i>)-5,10-methenyltetrahydrofolate
(6 <i>S</i>)-5-HCO-H ₄ folate	(6 <i>S</i>)-5-formyltetrahydrofolate

The following is an example of a mixture of stereoisomers at C-6:

(6-*ambo*)-5-HCO-H₄folate (6-*ambo*)-5-formyltetrahydrofolate

3. REFERENCES

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2. International Union of Pure and Applied Chemistry (1979) [*Nomenclature of organic chemistry, sections A, B, C, D, E, F and H*](#), (Rigaudy, J. & Klesney, S. R, eds) Pergamon Press, Oxford.
3. IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). [*Nomenclature and symbolism for amino acids and peptides. Recommendations 1983*](#). *Biochem. J.* **219**, 345-373 (1984); *Eur. J. Biochem.* **138**, 9-37 (1984); *Int. J. Pept. Prot. Res.* **24**, following p. 84 (1984); *J. Biol. Chem.* **260**, 14-42 (1985); *Pure Appl. Chem.* **56**, 595-624 (1984); *Spec. Period. Rep. Amino Acids Pept.* **16**, 387-410 (1985).

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