Pure & Appl. Chem., Vol. 59, No. 6, pp. 833–836, 1987.
Printed in Great Britain.

INTERNATIONAL UNION OF PURE
AND APPLIED CHEMISTRY
and
INTERNATIONAL UNION OF BIOCHEMISTRY

JOINT COMMISSION ON BIOCHEMICAL NOMENCLATURE*

NOMENCLATURE AND SYMBOLS FOR FOLIC ACID AND RELATED COMPOUNDS

(Recommendations 1986)

(Supersedes provisional version published 1965)

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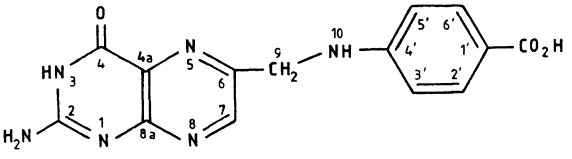
Nomenclature and symbols for folic acid and related compounds (Recommendations 1986)*

Synopsis — 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-glutamic acid 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.

CONTENTS

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. Marginal triangles ▲ indicate revised sections.



I. Pteroic acid

2. REVISED RECOMMENDATIONS

2.1 Parent compound

The compounds of this group are based on pteroic 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(3H)-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**.

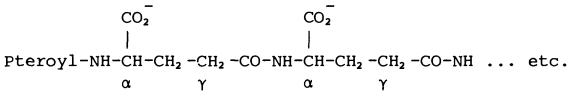
Comment

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.

*Draft prepared by Raymond L. Blakley, St. Jude Children's Research Hospital, Memphis, TN, USA

2.3 Glutamate conjugates

The compounds in which pteroic 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 tetrahydropteroyl-glutamates 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 (6S)-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 (±) 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 $N\cdots CH\cdots N$ structure.

Table 1

Substituent	Symbol	Formula	Substituent	Symbol	Formula
Formimino*	NHCH-	HN=CH-	Methylene	$-CH_2-$	$-CH_2-$
Formyl	HCO-	O=CH-	Methenyl*	$-CH^+-$	-CH= as component of
Methyl	CH_3-	CH_3-			$[>N-CH=N^+< \leftrightarrow >N^+=CH-N<]$

*The systematic names for HN=CH- and -CH= are iminomethyl (or formimidoyl) and methylidyne 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) Pteroate (or pteroyl or pteroic acid) is indicated by the three-letter symbol Pte.

(c) The pteroylglutamates and the corresponding acids are indicated by the symbols PteGlu, $PteGlu_2$, $PteGlu_3$, 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 H_2 or H_4 in front of the main symbol with an indication of the position if necessary, e.g. H_2folate, $H_4PteGlu_3$. 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) H_2, H_4 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:

(6S)-H_4folate	(6S)-5,6,7,8-tetrahydrofolate [(6S)-5,6,7,8-tetrahydropteroylglutamate]
(6R)-5,10-CH_2-H_4folate	(6R)-5,10-methylenetetrahydrofolate
(6S)-5-CH_3-$H_4PteGlu_3$	(6S)-5-methyltetrahydropteroyltriglutamate
(6R)-10-HCO-$H_4PteGlu_n$	(6R)-10-formyltetrahydrofolates [or (6R)-10-formyltetrahydropteroylpolyglutamates, if n = 1 is to be excluded]
(6R)-5,10-CH^+-H_4folate	(6R)-5,10-methenyltetrahydrofolate
(6S)-5-HCO-H_4folate	(6S)-5-formyltetrahydrofolate

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

(6-ambo)-5-HCO-H_4folate	(6-ambo)-5-formyltetrahydrofolate

3. REFERENCES

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