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Biosynthesis of 2-Amino-1-Hydroxy-Ethyl-Phosphonic Acid In *Acanthamoeba Castellanii*

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BIOSYNTHESIS OF 2-AMINO-1-HYDROXY-ETHYL- PHOSPHONIC ACID IN ACANTHAMOEBA CASTELLANII

FRIEDRICH HAMMERSCHMIDT

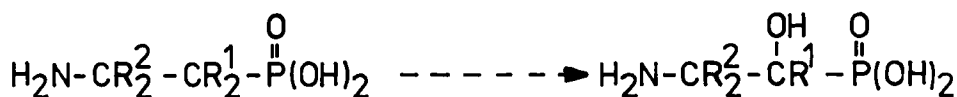
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Abstract The 2-amino-1-hydroxy-ethylphosphonic acid in *Acanthamoeba castellanii* (Neff) is biosynthesized by hydroxylating 2-amino-ethylphosphonic acid with removal of the C-1 pro-S hydrogen and replacing it by OH with retention of configuration.

INTRODUCTION

There are two natural products with a P-C-bond and a hydroxy-group on C-1: 2-amino-1-hydroxy-ethylphosphonic acid¹ (OH-AEP) 2 and the phosphonic acid of fosfazinomycins.²

The OH-AEP is most likely produced by hydroxylating either 2-amino-ethylphosphonic acid (AEP) 1 or phosphonoacetaldehyde.³ (1,1-²H₂)-, (2,2-²H₂)- and (1-²H)-AEP were prepared and added to the growth medium (1 mg/ml) of *Acanthamoeba castellanii* (Neff), which produces both AEP and OH-AEP. These two compounds were isolated from the amoeba and the isotopic composition was determined by MS.



		d_0	d_1	$d_2(\%)$
<u>1a</u>	$\text{R}^1 = {}^2\text{H}, \text{R}^2 = \text{H}$	<u>9</u>	<u>91</u>	
<u>b</u>	$\text{R}^1 = \text{H}, \text{R}^2 = {}^2\text{H}$	17	46	37
<u>c</u>	$\text{R}_2^1 = \text{H} + {}^2\text{H}$	53	47	

The AEP is taken up by the amoebas and incorporated into OH-AEP with virtually no kinetic isotope effect. The presence of doubly deuterated OH-AEP on feeding (2,2- ${}^2\text{H}_2$)-AEP 1b suggests direct hydroxylation of AEP. Oxygen-18 from ${}^{18}\text{O}_2$ is incorporated into the OH of OH-AEP.

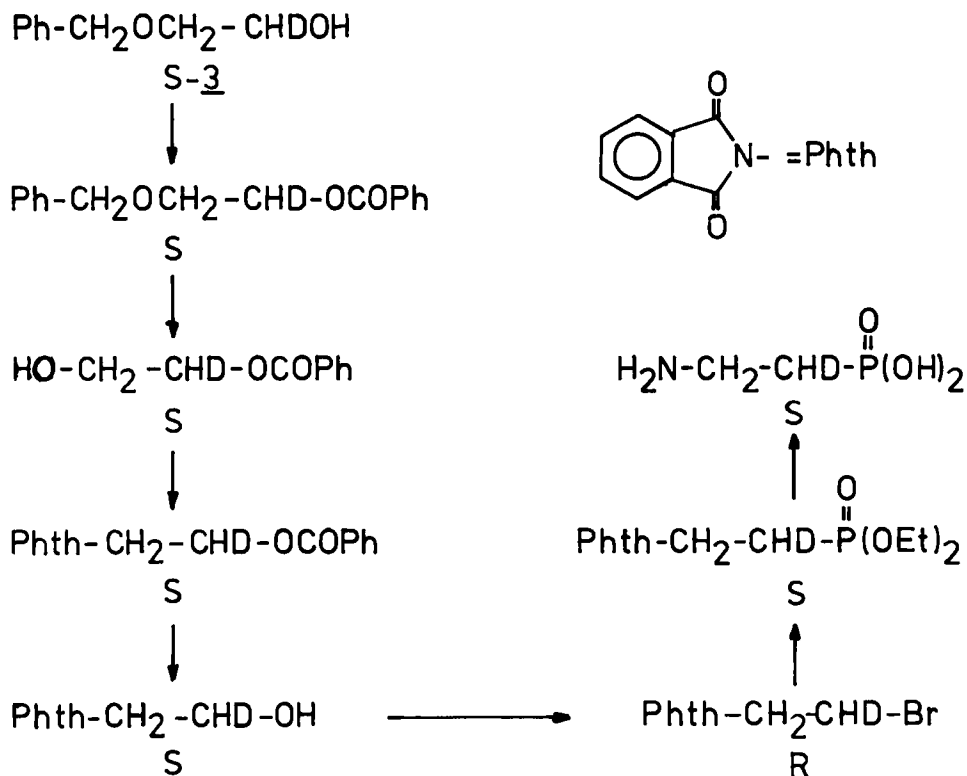
To study the stereochemical course of the hydroxylation, chirally labelled AEP was prepared and the absolute configuration of OH-AEP was determined.

SYNTHESIS OF (R)- and (S)-(1- ${}^2\text{H}$)-AEP

(S)-2-Benzoyloxy-(1- ${}^2\text{H}$)-ethanol 3 was prepared by HLAD⁴ catalyzed reduction of the corresponding deuterated aldehyde. It was used as starting material for the synthesis of (R)- and (S)-(1- ${}^2\text{H}$)-AEP given in scheme 1. The overall yield for the seven steps was 65 %. The ${}^2\text{H}$ of (S)-AEP (90% e.e.) is lost on hydroxylation, the ${}^2\text{H}$ of (R)-AEP (84% e.e.) is retained. Therefore the C-1 pro-S hydrogen of AEP is removed by the hydroxylase. The e.e.-value can be increased to about 95% for both chirally labelled AEP by using reaction flasks treated

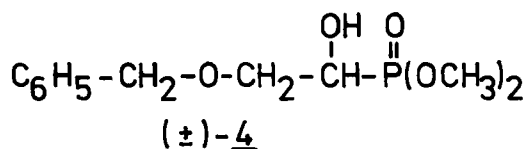
with trimethylsilylchloride/pyridine for the Arbuzow-reaction.

SCHEME 1



ABSOLUTE CONFIGURATION OF OH-AEP

Racemic 1-hydroxyphosphonate 4 was resolved with a chiral lactol.⁵ The S configuration is assigned to (+)-4 on the basis of a X-ray analysis. (R)-(-)-4 was transformed to (R)-OH-AEP which is identical with the natural product.



The hydroxylation occurs with retention of configuration at C-1 of AEP.

Further studies will concentrate on the biosynthesis of the phosphonic acid of fosfazinomycins A and B.

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