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### The Synthesis of Diphenyl Phosphonate Analogues of $\alpha$ -Amino Acids as Enzyme Inhibitors

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## The Synthesis of Diphenyl Phosphonate Analogues of $\alpha$ -Amino Acids as Enzyme Inhibitors

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$\alpha$ -Aminoalkylphosphonic acids are analogues of natural aminoacids and as such have been the subject of much research effort over past years<sup>1</sup>. The diphenyl esters of  $\alpha$ -aminoalkylphosphonic acids are particularly potent and show high selectivity as irreversible inhibitors of serine proteinases. Thus far,  $\alpha$ -aminoalkylphosphonic acid ester analogues of a number of aliphatic- and aromatic aminoacids have been prepared including valine, phenylalanine, tryptophan, and tyrosine<sup>2</sup>, and the basic aminoacids ornithine, lysine, etc.<sup>3</sup>. We have now also prepared the  $\alpha$ -diphenyl phosphonate analogues of the acidic aminoacids, aspartic and glutamic<sup>4</sup>. These have been examined as potential inactivators of serine proteinases exhibiting a P<sub>1</sub> specificity for aspartate and glutamate, e.g. *S. aureus* V8 protease and granzyme B.

Analogue	Apparent second-order rate constant (k/K <sub>i</sub> )	
	<i>S. aureus</i> V8 protease	GranzymeB
Acetyl-Glu <sup>P</sup> (OPh) <sub>2</sub>	$5.3 \pm 0.5 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$	N.I.
Acetyl-Asp <sup>P</sup> (OPh) <sub>2</sub>	$5.0 \pm 0.5 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$	N.I.

Initial results show that they function as irreversible inactivators of *S. aureus* V8 proteinase but show no activity towards granzyme B.

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