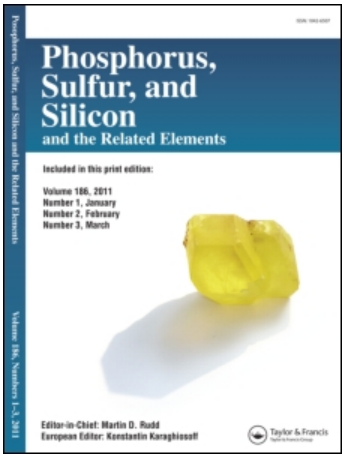

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Phosphonylated Acetylcholinesterase as Transition State Analogs: The Anticholinesterase Properties of Halomethylphosphonates

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To cite this Article Ashani, Y. and Segall, Y.(1987) 'Phosphonylated Acetylcholinesterase as Transition State Analogs: The Anticholinesterase Properties of Halomethylphosphonates', Phosphorus, Sulfur, and Silicon and the Related Elements, 30: 3, 814
To link to this Article: DOI: 10.1080/03086648708079304
URL: http://dx.doi.org/10.1080/03086648708079304

Phosphonylated Acetylcholinesterase as Transition State Analogs: The Anticholinesterase Properties of Halomethylphosphonates

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P.O.BOX 19 , NESS-ZIONA, ISRAEL

The $CH_3P(O)$ moiety of methylphosphonates of the type $CH_3P(O)(OR)X$, I, may play an important role in the effective binding to the appropriate hydrophobic patch in the active site of acetylchlinesterase (AChE), in analogous manner to the acetyl residue ,$CH_3C(O)$, of the substrate acetylcholine which determines substrate specificity.Since the substitution of halide atom for hydrogen in I is expected to introduce electronic,steric and hydrophobic changes,it was interesting to study the effect of such a substitution on both the inhibition of AChE and the stabilily of the phosphonylated enzyme.A significant decrease in the stability of the enzyme conjugates, $YCH_2P(O)$-(OisoPr)O-AChE (Y=Cl,Br,I) was observed in terms of an increase in the rate constants of the spontaneous and induced reactivations as well as the aging process relative to the non-substituted molecule where Y=H. The electron withdrawal effect of the halogen atom alone, cannot explain the changes in the anti-ChE properties of the halomethylphosphonates when compared to the non-substituted inhibitor. These results are in accord with the view that the phosphonylated enzyme may be considered as a transition-state analog for the hydrolysis of an acylated enzyme(Ashani and Green in "Studies in Organic Chemistry",pp 169-188,Vol 10, Elsevier ,1981). It is further concluded that in contrast to the OP-AChE conjugates the OP themselves cannot be rationalized in terms of transition-state analogs.