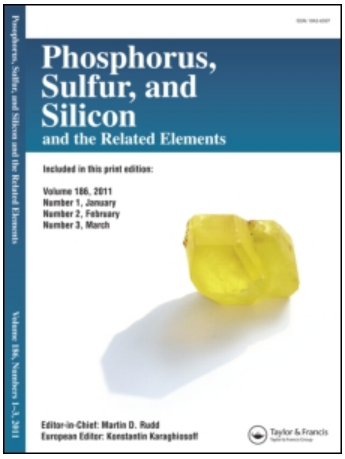


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Biological Activity of Aminomethanephosphonic Acids and Derivatives

Gerhard Hägele

To cite this Article Hägele, Gerhard(1999) 'Synthesis and Biological Activity of Aminomethanephosphonic Acids and Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 445 — 447
To link to this Article: DOI: 10.1080/10426509908546277
URL: http://dx.doi.org/10.1080/10426509908546277

Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 445-447
Reprints available directly from the publisher
Photocopying permitted by license only

Synthesis and Biological Activity of Aminomethanephosphonic Acids and Derivatives

GERHARD HÄGELE

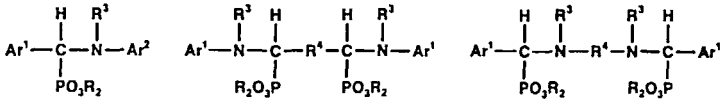
Institut für Anorganische Chemie und Strukturchemie Heinrich-Heine-Universität Düsseldorf, D-40225-Düsseldorf, Germany

Synthetic routes to α-aminomethanephosphonic acids and related structures are described. Particular attention is drawn towards aryl and fluoroaryl substituted α-aminomethanephosphonic and corresponding phosphinic acid alkylesters. Some comments on structural aspects and on biological activities are given.

Keywords: NMR; spectral analysis; simulation; PC programs

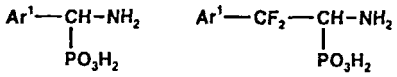
INTRODUCTION

A broad variety of aminophosphonic acids has attracted widespread attention in chemistry, medicine and agricultural sciences as analogues of natural aminoacids. This lecture describes synthetic routes to α-aminomethanephosphonic acids, corresponding esters and N-acylated compounds and emphasize structural types shown in **1** to **3**[1]:



1 **2** **3**

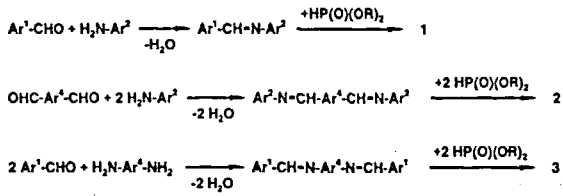
representing alkylesters of N- and C-arylsubstituted mono- and bisphosphonic acids (Ar^1, Ar^2: phenyl, naphthyl, anthranyl, benzpyryl, pyridyl; R^3: H, CH_3CO; R^4: C_6H_4, C_5H_3N, C_2H_4; R: H, alkyl). Monophosphonic acids are described with **4**[1] and **5**[2]:



The biological activity of such compounds is enhanced [3] by introducing fluorine or fluorinated substituents into aliphatic, aromatic or heterocyclic substituents ($C_6H_{4-i}F_i$, $C_5H_{3-i}NF_i$, trifluoromethyl- and trifluoromethoxibenzene derivatives $C_6H_4CF_3$, $C_6H_4OCF_3$). Replacing [4] phosphonate units $P(O)(OR)_2$ by analogous phosphinate structures like $P(O)(R^5)OR$ leads to a further increase of biological activity[3] e.g. in compounds like **6** to **8** shown below. Stereochemical aspects of compounds having one to four chiral centers situated at C- and P-atoms are discussed. Structures are identified by NMR [3,4], X-ray-diffraction [6] and molecular modeling[7].

Example 1

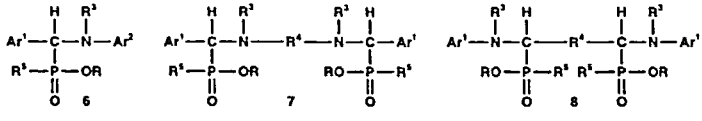
A useful practical route to compounds **1** - **3** involves two steps, the formation of (fluorinated) Schiff bases followed by addition of dialkylphosphite leading to **1** - **3** (R^3 = H):



Reaction conditions and catalysts required depend on the nature of substituents. In some cases diastereomeric induction is observed for the formation of **2** and **3**. Compounds **1** to **3** were tested[3,5]:as inhibitors for the mitochondrial NADH-dehydrogenase (Complex I). Molecular modeling studies for C_6H_5-NH-CH(p- $C_6H_4OCF_3$)$P(O)(OEt)_2$ were carried out to get some insight into the activity observed.

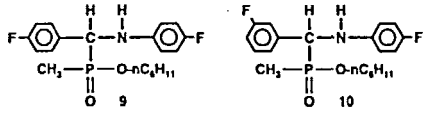
Example 2

Replacing the dialkylphosphite $HP(O)(OR)_2$ by alkylphosphonite $HP(O)(R^4)OR$ leads to corresponding phosphinicacid esters **6** to **8** (R^3: H; R^5: alkyl):



having either two or four chiral centers situated in C and P atoms resp..

Strongest inhibitor properties for the mitochondrial NADH-dehydrogenase (Complex I) were found [4,5] for the bis-p-fluorophenyl substituted aminomethane-P-methyl-phosphinicacid n-hexylester **9**:



Interactions of aminophosphonates and aminophosphinates with enzymes cyclooxigenase (COX-1) and 5-lipoxigenase (5-LO) of the arachidonicacid cascade which are involved in the biogenesis of prostaglandine and leukotrienes resp. were studied. Strongest inhibi-tor activity against COX-1 showed **9** while **10** was superior against 5-LO.

Acknowledgments

This study was supported by the Fonds der Chemischen Industrie, Academic Research Collaboration (ARC, DAAD), Bayer AG Monheim, Germany.

References

[1] a) U. Gruss and G. Hägele, Phosporus, Sulfur and Silicon **97,** 141 (1994). b) ibid. **111,** 159 (1996), c) D. St. C. Green, U. Gruss, G. Hägele, H. R. Hudson, L. Lindblom and M. Pianca, ibid. **113,** 179 (1996). d) U. Gruss, H. Dronia and G. Hägele, ibid. **77,** 318 (1993). e) G. Hägele, U. Gruss and H. Dronia, J. Fluor. Chem. **54,** 285 (1991).

[2] A. Haas, Dissertation, Heinrich-Heine-Universität Düsseldorf, 1997.

[3] U. Gruss, Dissertation, Heinrich-Heine-Universität Düsseldorf, 1997.

[4] a) N. P. Osthaus, Dissertation, Heinrich-Heine-Universität Düsseldorf, 1998.

[5] H. Weiss and T. Friedrich, Institut für Biochemie, Düsseldorf.

[6] a) M. McPartlin et al., University of North London. b) M. McPartlin et al., N. P. Osthaus, G. Hägele, to be published.

[7] a) H. Dronia, Dissertation, Heinrich-Heine-Universität Düsseldorf, 1995. b) H. Dronia, U. Gruss, G. Hägele, T. Friedrich and G. Hägele, J. of Computer-Aided Molecular Design **10,** 100 (1996).