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### Symmetrical and Unsymmetrical Bishophonate Esters Chemistry: Synthesis, Selective Hydrolysis, Isomerization

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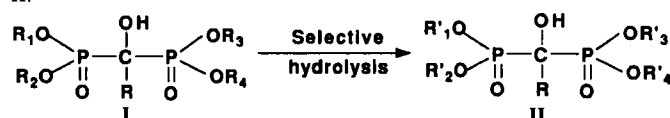
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## Symmetrical and Unsymmetrical Bisphosphonate Esters Chemistry : Synthesis, Selective Hydrolysis, Isomerization

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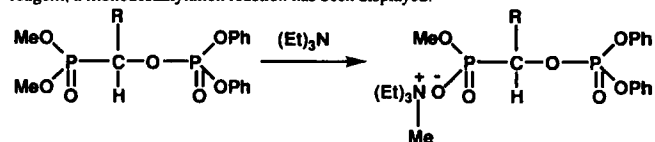
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Over the past few years, bisphosphonates have been receiving increased attention as a new class of pharmacologically active compound. As a continuation of our research program (1,2,3) in connection with the synthesis of bisphosphonate esters I, we present here some results about the synthesis of symmetrical and unsymmetrical bisphosphonate esters. These compounds were selectively hydrolyzed to give the following mono, di, tri and tetra acids II.



R = CH<sub>3</sub>, CH<sub>3</sub>-(CH<sub>2</sub>)<sub>n</sub>-, H<sub>2</sub>N-(CH<sub>2</sub>)<sub>n</sub>-, Ph-, Ph-CH<sub>2</sub>-. a) R<sub>1</sub> = R<sub>2</sub> = O-C(CH<sub>3</sub>)<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-O, R<sub>3</sub> = R<sub>4</sub> = CH<sub>3</sub>, R'<sub>1</sub> = R'<sub>2</sub> = H, R'<sub>3</sub> = R'<sub>4</sub> = CH<sub>3</sub>. b) R<sub>1</sub> = R<sub>2</sub> = Ph, R<sub>3</sub> = R<sub>4</sub> = CH<sub>3</sub>, R'<sub>1</sub> = R'<sub>2</sub> = Ph, R'<sub>3</sub> = R'<sub>4</sub> = H. c) R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = Ph, R<sub>4</sub> = CH<sub>3</sub>, R'<sub>1</sub> = R'<sub>2</sub> = R'<sub>3</sub> = Ph, R'<sub>4</sub> = H. d) R<sub>1</sub> = Ph, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = CH<sub>3</sub>, R'<sub>1</sub> = Ph, R'<sub>2</sub> = R'<sub>3</sub> = R'<sub>4</sub> = H.

Esters I are much less stable than the corresponding acids. These products undergo an isomerization simply by heating or catalysed by organic or mineral base. We have noted an acceleration of the isomerization reaction from bisphosphonate to phosphate-phosphonates when the R group is an attractive group as for instance an aromatic ring (R=Ph). When studying the isomerization reaction with these substrates and by using triethylamine as reagent, a monodesalkylation reaction has been displayed.



All the structures were characterised by elemental analysis, physicochemical constants, <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectroscopy.

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