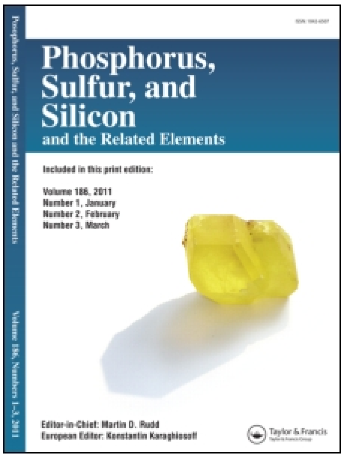

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New Bisphosphonates, Synthesis and Reactions

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To cite this Article Gross, H. , Ozegowski, S. , Haussdöhfer, S. , Keitel, I. , Schnell, M. and Costisella, B.(1990) 'New Bisphosphonates, Synthesis and Reactions', Phosphorus, Sulfur, and Silicon and the Related Elements, 49: 1, 191 — 194
To link to this Article: DOI: 10.1080/10426509008038938
URL: http://dx.doi.org/10.1080/10426509008038938

Phosphorus, Sulfur, and Silicon, 1990, Vols. 49/50, pp. 191–194
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NEW BISPHOSPHONATES, SYNTHESIS AND REACTIONS

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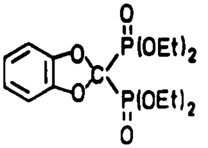
Abstract The synthesis and reactions of new bisphosphonates with different substituents in α-position as well as a new type of trisphosphonate are described.

Methanebisphosphonic acid and its derivatives are used as complexing agents, diagnostics and therapeutics and show interesting virustatic properties. For that reason we synthesized a number of new bisphosphonates and investigated their chemical properties.
First we prepared compounds with rigid structure of phosphonyl groups, e. g. 1, starting from pyrocatecholdichloromethyleneether. Compound 2 was prepared by cycloalkylation of methanebisphosphonate.



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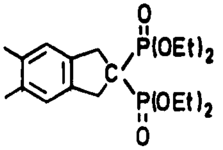

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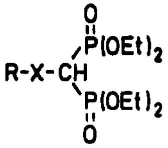
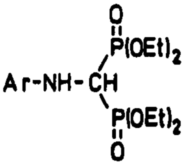


$R\text{-}X\text{-}CH[P(O)(OEt)_2]_2$

3

Bisphosphonates 3 may have different substituents in α-position. First we tried to extend the procedure of converting aminopyridines with orthoformate and diethyl phosphite (DEP) into bisphosphonates[1]. As a result, only aromatic amines with electron-attracting groups gave the bisphosphonates 4, which allowed to change the functional groups. So the p-nitroderivative of 4 was reduced to the amine and then with diethoxy-THF the pyrrolo derivative 5 was formed. The pyrrolo derivative 6



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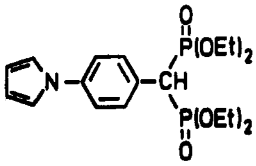

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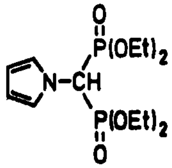

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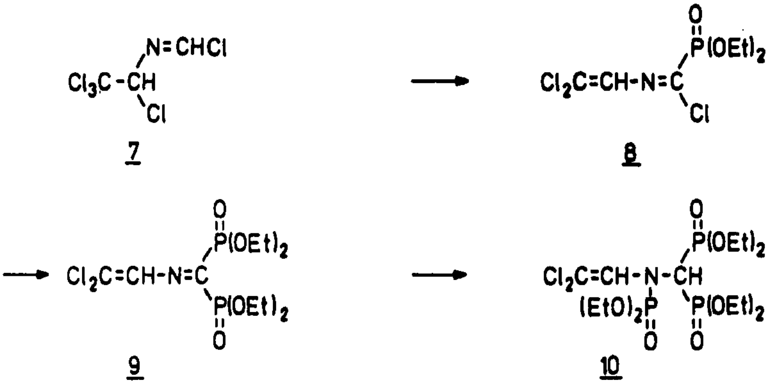
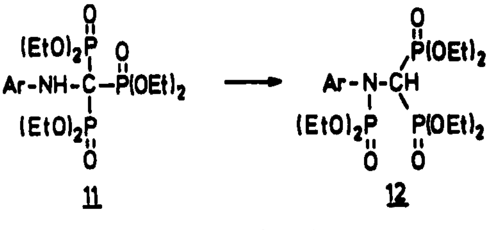
we prepared from L. Maier's[2] aminomethanebisphosphonate.

On treatment with triethyl phosphite (TEP) the chloroformamidine 7 primarily formed via internal redox



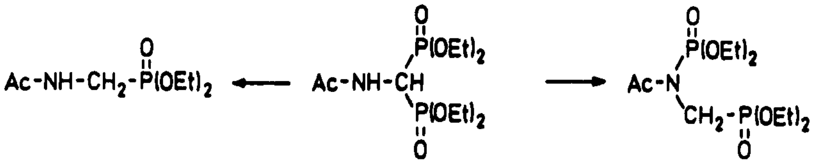
7 8 9 10

reaction the phosphonate 8, which is converted via 9 to the bisphosphonate 10. The last step is analogous to the rearrangement we observed when we tried to prepare the trisphosphonate 11 and isolated the bisphosphonate 12 instead.



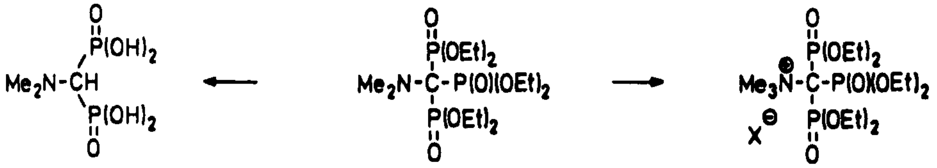
11 12

Similar rearrangement or splitting off a phosphonyl-group took also place on other systems. Thus, the bisphosphonate 14 prepared by W. Steglich[3] formed 15 when treated with ammonia, while sodium ethoxide formed 13 and triethyl phosphate.



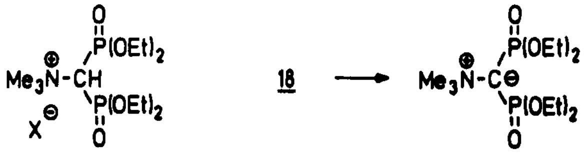
13 14 15

When we tried to hydrolyse V. P. Kuchar's trisphosphonate 17[4] one phosphono group was removed, forming the bisphosphonic acid 16. By N-methylation of 17 we



16 17 18

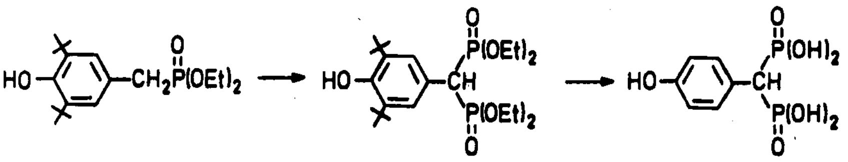
observed removal of one phosphonyl group to 19, if X^- is a nucleophilic anion. As a tosylate, 18 is stable, but dissolving it in ethanol affords trialkyl phosphate and



19 20

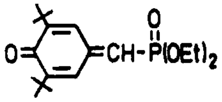
the stable N-ylide 20, which we previously prepared by deprotonation of 19.

Special structural requirements allow Arbusov-reactions with normally unreactive α-halobenzylphosphonates: the p-hydroxyphenylmethanephosphonate 21 with NBS and TEP



21 22 23

gave the bisphosphonate 22. Hydrolysis of 22 yields different products depending on the method used; e. g. with hydrochloric acid the tert.-butyl groups are removed, forming the 4-hydroxyphenylmethanebisphosphonic acid 23, which can be further substituted in the aromatic ring. By oxidation of the phosphonate 21 or 22 we prepared the quinonemethides 24 or 25, respectively.



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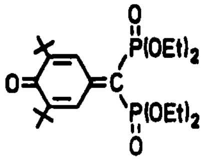

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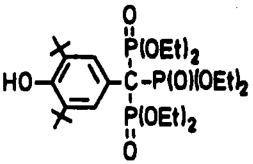

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Treating 24 with DEP, the bisphosphonate 22 was formed. Similarly, 25 was converted to the trisphosphonate 26, a remarkably stable product, which is the only known phosphonate of this type.

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