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STEREOSPECIFIC CONVERSION OF CYCLIC PHOSPHOROTHIOATES INTO CHLOROPHOSPHATES

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Summary : The reaction of the individual diastereoisomeric cyclic phosphorothioates **2a, 2b** in the trans-2,4,7-trioxa-3-phosphabicyclo (4.4.0) decane and **4a, 4b** in the trans-2,4,7-trioxa-3-phosphabicyclo (4.3.0) nonane series with sulphuryl chloride affords the corresponding sulphenyl chlorides **5a, 5b, 6a, 6b** with retention of the configuration of the phosphorus atom. The reaction of the latter with phosphorus trichloride leads stereospecifically to the chlorophosphates **7a, 7b, 8a** and **8b** with full retention of configuration at phosphorus.

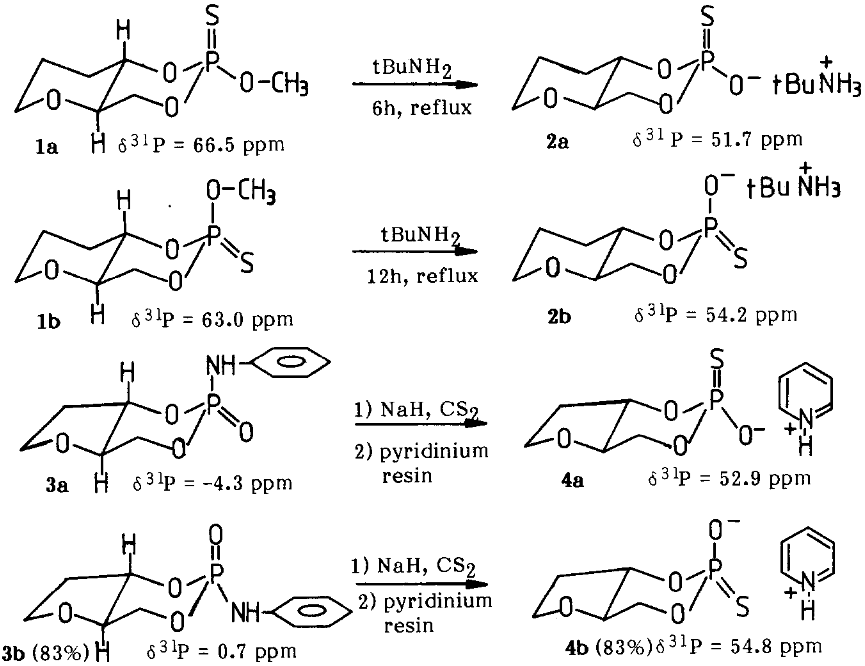
Cyclic chlorophosphates in the 1,3,2-dioxaphosphorinan-2-one series are usually obtained by the condensation of a diol with phosphorus oxychloride.[1] In the case of dissymetric diols, depending on the experimental conditions, the formation of only one[2] or two diastereoisomeric products (epimeric at phosphorus)[3] has been observed. Unfortunately this method is not adequate for the preparation of chlorophosphates which would lead to the formation of a sterically strained dioxaphosphorinane ring.[4]

We wish to describe herein a convenient route to the individual diastereoisomeric cyclic chlorophosphates **7a, 7b** , **8a** and **8b** of the type mentioned above, which in turn can be used in the synthesis of various derivatives by nucleophilic substitution of the chlorine atom.

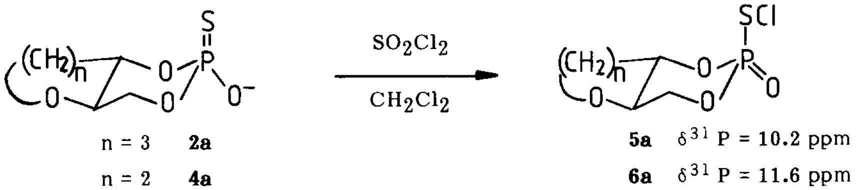
Indeed, in the context of studies[5] about the preparation and reactivity of oxophosphoranesuphenyl chlorides (RO)(R'O)P(O)SCl towards tricoordinated phosphorus compounds, we were able to perform the stereospecific synthesis of these chlorophosphates under very mild conditions.

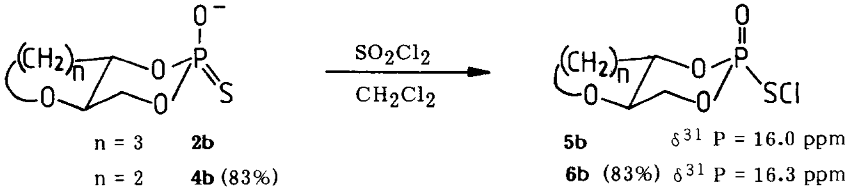
If it was observed that the reaction of phosphorus trichloride with acyclic sulphenyl chlorides leads exclusively to deoxygenation products, the same reaction with cyclic compounds was found to be non-selective.[5b] Thus, the reaction of phosphorus trichloride with cis-and trans-2-chlorothio-4-methyl-1,3,2-dioxaphosphorinan-2-ones leads to both deoxygenation and desulphurisation products with loss of the diastereoisomeric purity. However, in the trans-2,4,7-trioxa-3-phosphabicyclo (4.4.0) decane and trans-2,4,7-bicyclo (4.3.0) nonane series, in contrast to the previous experiments but under the same reaction conditions, we were able to obtain the products of desulphurisation almost exclusively, i.e. the cyclic chlorophosphates **7a, 7b** and **8a, 8b**.

The diastereoisomeric salts **2a** and **2b** were obtained from the methylthiophosphates[6] **1a** and **1b** by reaction with terbutylamine,[7] whereas the salts **4a** and **4b** were prepared from the phosphoroanilidates[8] **3a** and **3b**, using a slight modification of a known procedure for 3',5'-nucleotides.[9]



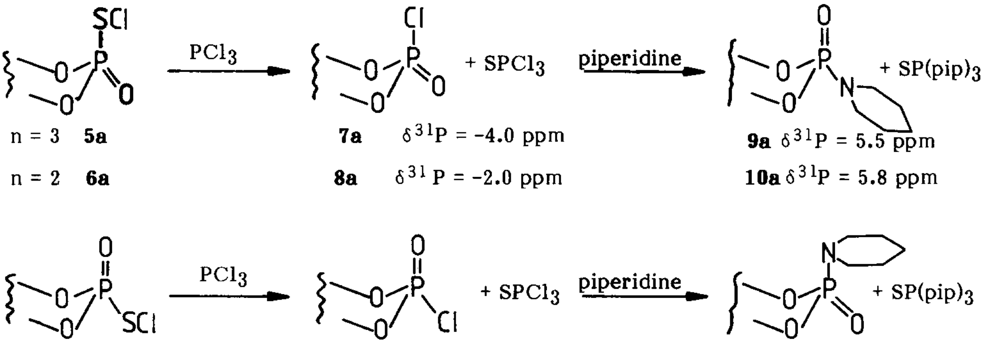
The reaction of these phosphorothioates (**2a**, **2b**, **4a** and **4b**) with the equimolar amount of sulphuryl chloride in methylene chloride below 0°C leads quantitatively (as judged by ^{31}P NMR spectra of the reaction mixtures) to the corresponding oxophosphoranesulphenyl chlorides **5a**, **5b**, **6a** and **6b** with full retention of configuration of the phosphorus atom.





The configurational assignments of **5a**, **5b**, **6a** and **6b** were made by comparison of their ^{31}P chemical shifts (positive downfield from 85% H_3PO_4) to those at 13.0 ppm (for P=O axial) and 9.2 ppm (for P=O equatorial) reported for the corresponding sulphenyl chlorides in the 4-methyl-1,3,2-dioxaphosphorinane series.[10]

Without isolation of the sulphenyl chlorides, treatment of the reaction mixtures with phosphorus trichloride at -40°C, -20°C stereospecifically affords the chlorophosphates **7a**, **7b**, **8a** and **8b**. Only in the case of **6a** was it possible to detect by ^{31}P NMR the presence of about 9% of the deoxygenation product.



n = 3 **5a** **7a** $\delta^{31}P = -4.0$ ppm **9a** $\delta^{31}P = 5.5$ ppm

n = 2 **6a** **8a** $\delta^{31}P = -2.0$ ppm **10a** $\delta^{31}P = 5.8$ ppm

n = 3 **5b** **7b** $\delta^{31}P = -2.6$ ppm **9b** $\delta^{31}P = 9.7$ ppm

n = 2 **6b** (83%) **8b** (83%) $\delta^{31}P = -2.0$ ppm **10b** (83%) $\delta^{31}P = 4.0$ ppm

The confirmation of the configurational assignments of the chlorophosphates **7a, 7b** and especially **8a, 8b** (which have the same ^{31}P chemical shift) was accomplished after their transformation into the phosphoramidates **9a, 9b, 10a** and **10b.** These derivatives can be easily isolated and purified by column chromatography. The analysis of their ^{31}P and ^{1}H (350 MHz) NMR spectra[11] allowed us to ascribe the indicated configurations to the phosphorus atom and to relate them to those of the starting chlorophosphates. The nucleophilic substitution of the chlorine atom by amine is indeed well known to proceed with complete inversion of configuration at phosphorus.[12]

The present results suggest that this procedure, without isolation of the intermediate products, may be a convenient route for the preparation of the corresponding 3',5'-cyclic chlorophosphates in nucleotide field starting form the known phosphorothioates. This problem is currently being investigated.

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NOTES AND REFERENCES

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