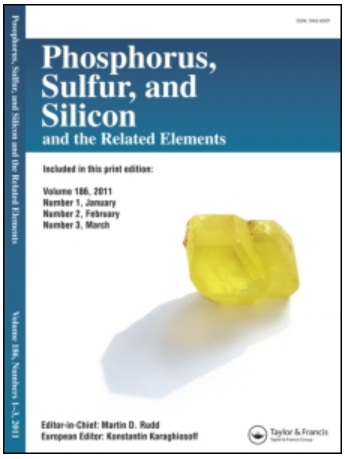

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Study of Intramolecular Staudinger Reaction and Reductive Cyclisation in 4-Alkoxy-1,3,2-Oxazaphosphorinane Ring Formation : Synthesis of Bicyclic Preactivated Analogues of Cyclophosphamide

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STUDY OF INTRAMOLECULAR STAUDINGER REACTION AND REDUCTIVE CYCLISATION IN 4-ALKOXY-1,3,2-OXAZA-PHOSPHORINANE RING FORMATION : SYNTHESIS OF BICYCLIC PREACTIVATED ANALOGUES OF CYCLOPHOSPHAMIDE

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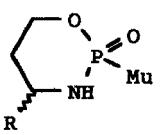
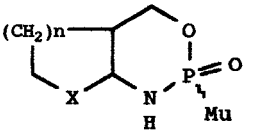
Abstract The synthesis of 4-alkoxy-1,3,2-oxaza-phosphorinanes in the 3-oxo-2-aza-4,9-dioxa-3-phosphabicyclo-(4.3.0)nonane and 3-oxo-2-aza-4,10-dioxa-3-phosphabicyclo-(4.4.0)decane series has been performed starting from azidoalcohols using intramolecular Staudinger reaction and reductive cyclisation.

INTRODUCTION

Cyclophosphamide (CP), a widely used anticancer and immuno-suppressive agent, is itself a prodrug that is activated by C_4-hydroxylation in the liver. The resulting 4-hydroxycyclo-phosphamide (4-hydroxy-CP) undergoes ring opening, followed by generation of the cytotoxic phosphoramide mustard and acrolein by β-elimination. Acrolein is responsible for side effects which are dose-limiting in cyclophosphamide therapy. For this reason, many attempts have been made recently to trap acrolein or avoid its production during clinical treatment.[1,2] We are ourselves[3] engaged in the synthesis of bicyclic preactivated analogues of cyclophosphamide (4-substituted oxazaphosphorinanes) which could give phosphoramide mustard without hepatic activation and which meet the preceding criterion.



Mu = $-N(CH_2CH_2Cl)_2$
R = H CP
R = OH 4-hydroxy-CP
X = O, S



In connection with this work we describe below results concerning the use of *Staudinger reaction* and *reductive cyclisation* in order to realise the 4-alkoxy-1,3,2-oxazaphophorinane ring formation in the 3-oxo-2-aza-4,10-dioxa-3-phosphabicyclo[4.4.0]decane and 3-oxo-2-aza-4,9-dioxa-3-phosphabicyclo[4.3.0]nonane series.

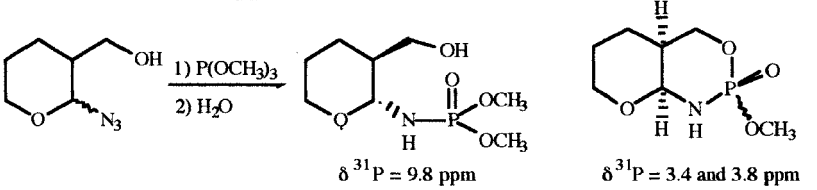
CYCLISATION USING THE STAUDINGER REACTION

If there are some examples of 1,3,2-oxazaphospholane ring formation from a β-azidoalcohol by reaction with a tricoordinated phosphorus compound, the synthesis of the 1,3,2-oxazaphosphorinane ring from a γ-azidoalcool was studied[4] to a lesser extent.

Cyclisation studies were made on 2-azido-3-hydroxy-methyltetrahydropyran by reaction with trimethylphosphite, chloro[N,N-bis(methylethyl)amino]methoxyphosphane and chloro-[bis[N,N-bis(methylethyl)amino]phosphane.

Reaction with trimethylphosphite

Addition of an equimolar amount of trimethylphosphite to a solution of 2-azido-3-hydroxymethyltetrahydropyran in chloroform at 25°C is followed by a slow nitrogen evolution. Surprisingly, heating at reflux during one hour is necessary to see the complete disappearence of the azido group. ^{31}P NMR spectrum at this stage shows a complex mixture. Water addition is followed by the appearence of three major signals at 9.8, 3.8 and 3.4 ppm.



$\delta^{31}P = 9.8$ ppm $\delta^{31}P = 3.4$ and 3.8 ppm

Structural elucidation of the compounds of the reaction shows that the *trans* azidoalcohol gives a ring opened compound whereas the *cis* isomer leads to bicyclic phosphoramidates whose configurations were assigned after ^{31}P and ^{1}H NMR study.

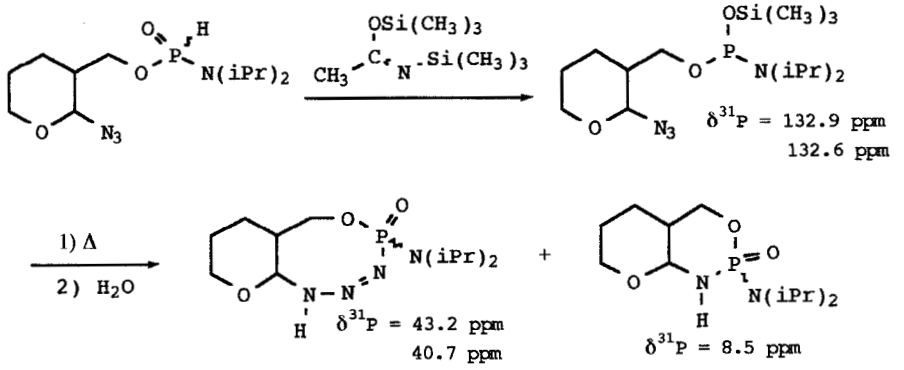
Reaction with chloro[N,N-bis(methylethyl)amino]methoxy-phosphane

The low temperature reaction of chloro[N,N-bis(methylethyl)-amino]methoxy-phosphane, a tricoordinated phosphorus derivative largely used in nucleotide chemistry, with the 2-azido-3-hydroxymethyltetrahydropyran yields the expected phosphoramidite. Heating of the reaction mixture, necessary for the complete disappearence of the intermediate phosphoramidite, gives however a very complex mixture, resulting probably from ligand exchange at the tricoordinated phosphorus compounds level before reaction with the azido group.

Reaction with chlorobis[N,N-bis(methylethyl)amino]phosphane

In order to avoid undesirable exchange reactions, we decided to prepare an intermediate phosphonate which could be converted *in situ* into the corresponding tricoordinated phosphorus compound by a silylating agent.

Thus, condensation at low temperature of one equivalent of chlorobis[N,N-bis(methylethyl)amino]phosphane with the azidoalcohol followed by hydrolysis gives a mixture of the four diastereomeric phosphonates. The reaction of the *cis* phosphonate with bistrimethylsilylacetamide yields the corresponding silyl phosphite as a mixture of two diastereomers.

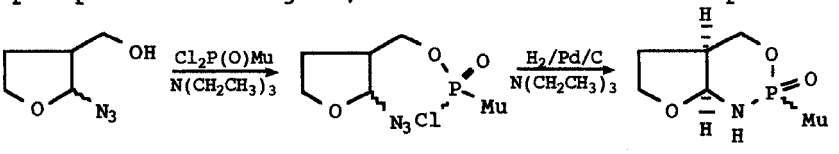


Heating and then hydrolysis gives, alongside the expected cyclic phosphoramidates, compounds having a phosphotriazene structure (tentatively assigned after examination of infrared, mass and NMR spectra). Very few

examples of relatively stable linear phosphotriazenes are known,[5] and it is the first time to our knowledge, that such a structure is included in a stable cyclic compound.

REDUCTIVE CYCLISATION. 3-[N,N-BIS(2-CHLOROETHYL)AMINO]-3-OXO-2-AZA-4,9-DIOXA-3-PHOSPHABICYCLO(4,3,0)NONANES SYNTHESIS

The reaction of the mixture of *cis* and *trans* isomers of 2-azido-3-hydroxymethyltetrahydrofuran with N,N-bis(2-chloroethyl)aminophosphoryldichloride in the presence of one equivalent of triethylamine gives the monochloridate. Reduction of the azido group by hydrogen, catalyzed by palladium on charcoal in the presence of one equivalent of triethylamine, leads to only two *cis* bicyclic cyclophosphamide analogues, instead of the four expected.



The interpretation of these results and the discussion of the isomerisation mechanism is based upon the known epimerisation of 4-substituted preactivated analogues of cyclophosphamide in acidic medium[2] and the existence of a dynamic equilibrium of some spirocyclic aminals.[6]

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