Pergamon

Tetrahedron, Vol. 52, No. 8, pp. 2995-3004, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00017-8

Cyclenphosphine Sulfide : Fluxional Behaviour and Ambident Reactivity.

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Abstract : The cyclenphosphine sulfide is prepared by reaction of molecular sulfur on cyclenphosphorane, obtained by transaminating hexamethylphosphorous triamide with 1,4,7,10-tetraazacyclododecane (cyclen). The fluxional behaviour of this compound is characterized by NMR ^{13}C and ^{31}P spectroscopy. Treatment of the titled compound by n-BuLi, followed by reaction with various electrophiles leads to either N- or S- alkylation according to the nature of the reactant.

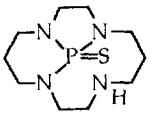
INTRODUCTION

Recently, many metal complexes of tetraazamacrocycles have been synthesized and characterized. These compounds present an increasing number of applications especially in diagnostic and therapeutic medicine because of their favourable thermodynamic and kinetic stability[1, 2, 3]. So, the problem of the selective mono N-alkylation of tetraazamacrocycles remains an interesting challenge : in most derivatives, the macrocycle bears four identical pendant arms and only a few reports of compounds, carrying side chains of different nature on the nitrogen atoms, have been described[4, 5, 6].

In a previous paper we reported the mono N-alkylation of tetraazamacrocycles[7] *via* a phosphoryl triprotection, leading to a series of mono N-functionalized adducts.

The chemistry of the homologous thiophosphoramides is, on the contrary, not very developed and, to our knowledge, only compounds 1 and 2 have been previously reported as a ligand (1), and a potential bidentate asymmetric ligand (2) respectively [8, 9].

1



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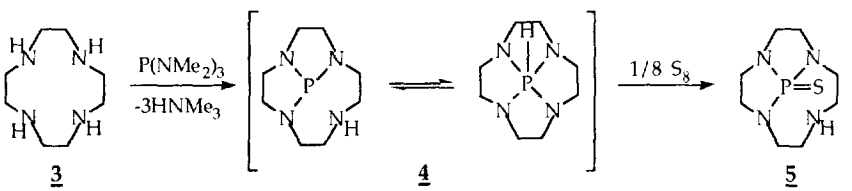
In this work, in addition to structural studies, the reactivity of the thiophosphoramide derivative of cyclen 3, towards electrophilic agents is reported.

RESULTS AND DISCUSSION

The thiophosphoramide 5 of cyclen 3 was obtained in good yields after transaminating hexamethylphosphorous triamide with 3, followed by the reaction of molecular sulfur (Scheme I).



3 4 5

Scheme I

Structural data :

The ^{13}C NMR spectrum at 293 K indicates the presence of four types of carbon atoms, three of them being coupled with phosphorus (Chart 1). At higher temperature, 335 K, no spectral modification is observed. The ^{1}H NMR spectrum, recorded in $CDCl_3$ at room temperature, exhibits a group of six poorly resolved multiplets between δ = 2.3 and 3.6 ppm, corresponding to anisochronous hydrogen atoms, located on different carbons of the macrocycle. These two results are in agreement with the structure 5.

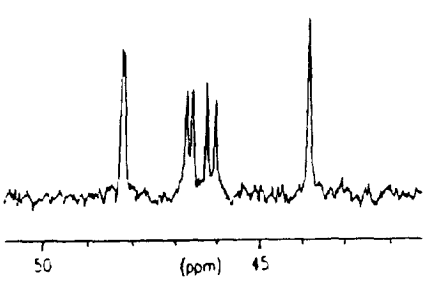
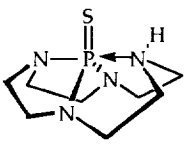


Chart 1

The behaviour of 5 in its ^{31}P spectrum is rather unusual. In $CDCl_3$, one signal at δ = 31.4 ppm, intermediate between a thiophosphoramide compound (60 ppm < δ < 80 ppm)[10] and a

pentacoordinated phosphorus (δ = -21.3 ppm)[11] is observed. This signal is progressively shifted downfield either on dilution or on increasing the temperature. Unlike cyclenphosphine oxide[11] this shift is weak. The infrared spectrum in CCl_4 exhibits two bands ; the associated N-H and the free N-H stretching bands are observed at 3136 and 3282 cm^{-1} respectively. The intensity of this hydrogen bonded N-H is dependent on concentration and disappears on dilution; these results are in agreement with an intermolecular association. The low free N-H band frequency indicates a weakening and consequently an elongation of the N-H bond[12, 13]. So the ^{31}P NMR and IR spectra suggest a strong interaction between nitrogen and phosphorus atoms (Scheme II) ; effectively, transannular interactions are known to be favoured in eight membered rings.



Scheme II

In a protic solvent, the ^{13}C NMR spectrum is considerably modified. In CD_3OD, two broad signals at δ = 44.9 and 47.9 ppm are observed between 203 K and 333 K while a ^{31}P NMR signal at δ = 17 ppm is recorded. In D_2O the ^{13}C NMR spectrum presents two peaks at δ= 46.1 and 47.1 ppm and a signal is obtained at δ = 8.5 ppm for the ^{31}P NMR spectrum. In these two solvents, in contrast to the behaviour of cyclen phosphine oxide [11], the ^{31}P chemical shifts are only slightly dependent on temperature and dilution. However, a temperature dependent ^{13}C NMR spectrum of 5 is obtained in undried $CDCl_3$. So at 220 K, the four broadened signals are still observed (*vide supra*) ; above 260 K, the signals coalesced to give two peaks slightly splitted at δ = 44.7 and 47.3 ppm which become well resolved at higher temperature (Chart 2). This evolution indicates an exchange process between nitrogens ; this fluxional behaviour requires a proton transfer between the two apical nitrogen atoms.

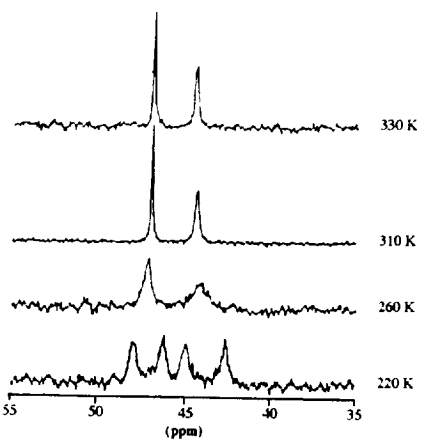
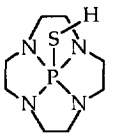


Chart 2

The tautomeric form P-SH 6, involving a pentacoordinated phosphorus, could be considered in this process, although it is not detected either in ^{13}C or ^{31}P NMR spectra. Moreover, semi empirical calculations in gas phase (AM1 formalism) indicate that the most stable structure is 5 ($\Delta E = 41.7$ kJ.mol^{-1}).



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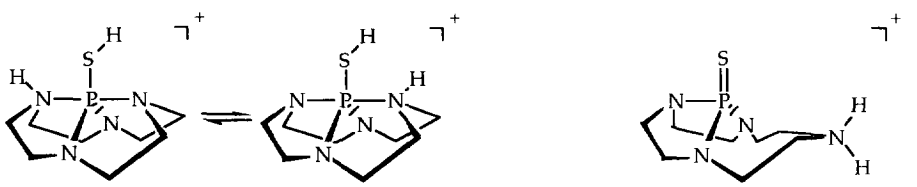
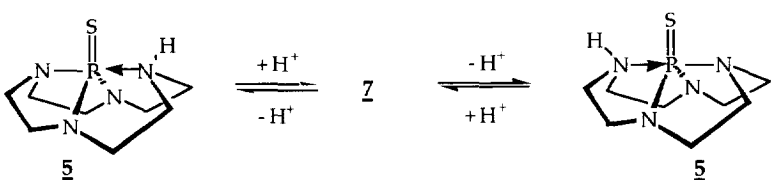
In order to explain these results we must assume that the protic solvent participate in this exchange process ; certainly the equatorial nitrogens are not protonated, according with the lack of basicity described for those atoms, and with the existence of the interaction nitrogen-phosphorus[14, 15, 16]. In HCl solution, sharp peaks are obtained in ^{13}C NMR as two doublets at $\delta = 44.1$ ppm ($J_{PC} = 8.51$ Hz) and $\delta = 44.7$ ppm ($J_{PC} = 5.5$ Hz). Futhermore, a ^{31}P NMR signal at $\delta = -12.5$ ppm is consistent with a pentacoordinated structure 7, exchanging rapidly the N-H proton and excluding structure 8. According to the acidity of the medium, 5 and 7 derivatives can simultaneously be observed in ^{31}P NMR ; addition of an excess of sodium hydroxyde induces disappearance of compound 7 in benefit of 5.



7 8

So the exchange process in protic solvent involving a proton transfer between the apical nitrogen atoms is catalysed by hydrogen donors *via* a sulfur protonation (Scheme III).



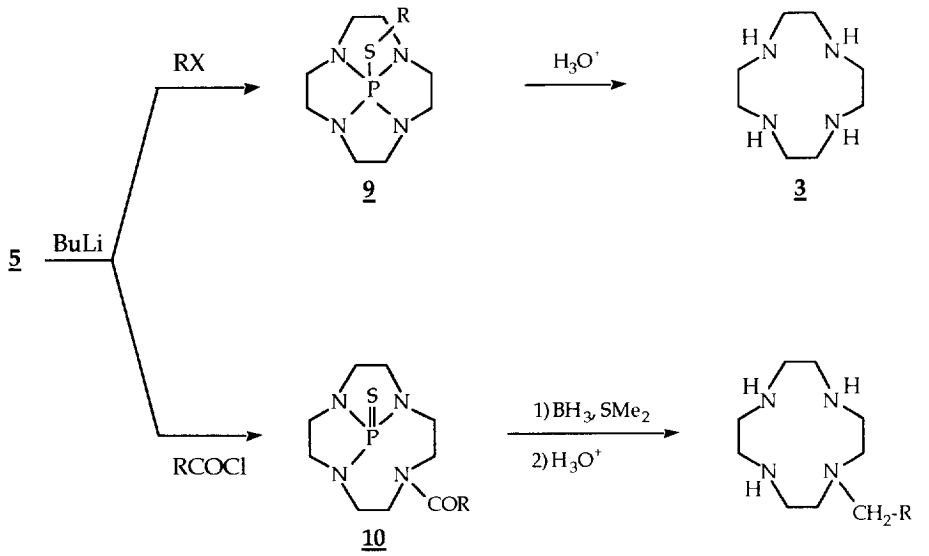
5 7 5

Scheme III

Reactivity:

The action of an alkylating reagent, in presence of a base as proton scavenger, leads, according to the electrophile either to S-alkylated or to N-alkylated derivatives (Scheme IV). This

behaviour is in contrast with the cyclen phosphine oxide one, with which only N- alkylation is observed[7]. Yields improvements require the use of BuLi in THF before addition of the electrophile. The acidic hydrolysis of the intermediate 9 leads to the recovery of the cyclen 3; intermediates 10 give in good yields mono N- alkylated cyclen after BH_3/SMe_2 reduction, followed by an acidic hydrolysis.

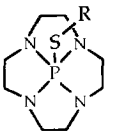
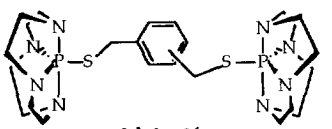
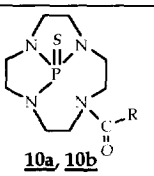
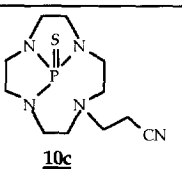


Scheme IV

With alkyl halide, only S-alkylation is obtained (Table I). ^{31}P NMR spectra are in good agreement with a fully pentacoordinated phosphorus (δ = -19 ppm). ^{13}C NMR spectra of all S-alkylated derivatives exhibit a unique doublet for all the carbons of the cycle, and heteronuclear $^{31}P/^{13}C$ decoupling experiments confirm it. Moreover, two groups of peaks are observed in ^{1}H NMR for the hydrogens of the cycle. These results suggest a pseudo square-pyramidal structure or more probably a rapid pseudorotating trigonal bipyramidal structure which makes all the carbon of the ring equivalent. This phenomenom is already described by Richman for the cyclen fluorophosphorane[17] and cyclen phosphorane[18].

Under similar conditions with acyl chlorides and simply heating in ethanol with acrylonitrile, only N-alkylation is reached (Table I). ^{31}P NMR spectra are consistent with the chemical shifts observed for tetracoordinated derivatives[9,10]. So, the substitution of an hydrogen atom by an alkyl or acyl group at the nitrogen leading to 10 results in the disappearance of the strong P←N-H interaction observed in 5, because of geometrical factors.

Table 1 : *Alkylation of* 5

Electrophilic reagent	Entry	End product	^{31}P (δ ppm)	Yield (%)
$C_6H_5CH_2$-Br	9a	 9a, 9b, 9c	-18.83	90
CH_3-I	9b		-19.55	90
n-C_3H_7-I	9c		-19.10	97
o-dibromoxylene	9d	 9d, 9e, 9f	-19.74	98
m-dibromoxylene	9e		-18.77	97
p-dibromoxylene	9f		-18.71	98
C_6H_5-COCl	10a	 10a, 10b	+84.22	98
C_2H_5-COCl	10b		+83.92	97
CH_2=CH-CN (a)	10c	 10c	+79.59	93

(a) see Experimental Section

The first step of the alkylation reaction consists obviously in the formation of an anion. This species present a doublet at δ = 44,5 ppm (J_{PC} = 9.2 Hz) in ^{13}C NMR spectrum in CD_2Cl_2 and for ^{31}P NMR spectrum only one peak is observed at δ = -51 ppm, consistent with a pentacoordinated phosphorus. So, the structure of the anion 11 draws near to the cyclen(alkylthio)phosphorane 9. The optimized structure of 11 in gas phase, calculated in AM_1 formalism agrees with this hypothesis [19](Figure I).

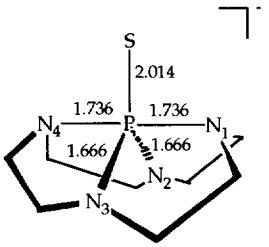


Figure I: Main parameters of anion 11.
Bonds lenghts are in angström.

This geometry, characterized by a pentacoordinated phosphorus, exhibits two identical P-N apical bonds (1.736 Å), longer than those calculated for the PSH form 6 (1.670 Å); P-S bond length (2.014Å) appears between a double and a single bond. Therefore we can conclude to an electronic delocalization on the S-P-N chain. The equatorial nitrogens appear to be more strongly bonded than apical ones with phosphorus. Hence, nitrogens N1 and N4 remain more reactive and constitute the hard nucleophilic center (reaction with acyl chlorides) ; on the other hand, the HOMO localization on sulfur lone pair allows to identify this atom as a soft nucleophilic center able to react with soft electrophile as alkyl halides.

CONCLUSION

Our results have to be compared with previous work done by Richman and Kubale[11] on cyclenphosphine oxide. In both cases, the hydrogen exchange between apical nitrogen atoms is catalyzed by protic solvent ; however, a protonated intermediate 7 is detected in acidic medium. The cyclenphosphine oxide gives rise to important monomer-dimer equilibrium which appears less pronounced for 5. In chloroform-d solution, exchange process between carbon sites is observed for cyclenphosphine oxide but in the same conditions, this phenomenon does not occur for the sulfide 5. However, the position of the free N-H stretching band 3282 cm^{-1} of cyclenphosphine sulfide suggests a bond weakening for 5. These results are the consequence of both geometric and electronic effects : on one hand, transannular P-N bonding is favoured by a eight membered ring, on the other hand the 3d orbitals of phosphorus atom are available for a strong interaction with the nitrogen lone pair.

For cyclenphosphine sulfide this interaction is responsible for hydrogen exchange process catalysed by hydrogen donors (fluxional behaviour) and for the ambident reactivity of 5 and its anion 11. From the organic synthesis point of view, 5 is easy to prepare and can constitute a interesting alternative way to introduce, with good yields, pendent arms on nitrogen atom. Further investigations on higher homologous of cyclenphosphine sulfide are in progress.

EXPERIMENTAL SECTION

Instrumentation: Infrared spectra were obtained on a Bomem Michelson 100 spectrophotometer. All ^{1}H and ^{13}C NMR were recorded on Brucker AC300 spectrometer (75.47 MHz for C) ; chemical shifts are given in ppm downfield from external TMS reference. ^{31}P NMR spectra were recorded on JEOL FX 100 spectrometer (40.26 MHz) and Brucker AC300 spectrometer (121.49 MHz) ; chemical shifts are given in ppm downfield from external 85% H_3PO_4. Mass spectra were obtained on a Hewlet Packard GC/MS HP 5995C and High Resolution Mass Spectra are recorded using ZabSpecETOF EI+ VG analytical. All semi empirical calculations were performed in AM_1 formalism with HyperChem® 2 for Windows.

All the reactions were run under nitrogen using freshly distilled and dry solvents.

- **Cyclenphosphine sulfide 5 :** the tetraazamacrocycle **3** (1 mmol) in toluene (30mL) was refluxed with hexamethylphosphorous triamide (1 mmol) until dimethylamine evolution ceased. After cooling to room temperature, a suspension of molecular sulfur (1/8 mmol S_8) in 20 mL of toluene, was dropwise to the solution of **4**. The resulting mixture is then refluxed for three hours. After evaporation of the solvent, the residue is solubilized in CH_2Cl_2. After filtration and evaporation a pale yellow powder is obtained (95% yield), mp 202°C. ^{31}P NMR : 31.4 ppm ($CDCl_3$), +32.9 ppm (CD_2Cl_2), +17.4 ppm (CD_3OD), +8.4 ppm (D_2O). ^{13}C NMR ($CDCl_3$) : 43.87 (2 N-$\underline{C}H_2$), 46.18 (d, 2 N-$\underline{C}H_2$, J_{PC} = 16Hz), 46.69 (d, 2 N-$\underline{C}H_2$, J_{PC} = 11.3Hz), 48.24 ppm (d, 2 N-$\underline{C}H_2$, J_{PC} = 4.3Hz). ^{13}C NMR (CD_3OD) : 47.3 (4 N-$\underline{C}H_2$), 44.9 ppm (4 N-$\underline{C}H_2$). ^{13}C NMR (D_2O) : 47.61 (4 N-$\underline{C}H_2$), 46.16 ppm(4 N-$\underline{C}H_2$). ^{1}H NMR ($CDCl_3$) : 2.44 (m, 2H), 2.66 (m, 2H), 2.87 (m, 1H), 3.07 (m, 4H), 3.21 (m, 3H), 3.40 (m, 4H), ≈ 7.2 ppm (N-H). IR (CCl_4) : $\upsilon_{N\text{-}H\ free}$ = 3282 and $\upsilon_{N\text{-}H\ bonded}$ = 3136 cm^{-1}. IR ($CDCl_3$) : $\upsilon_{N\text{-}H\ free}$ = 3277 and $\upsilon_{N\text{-}H\ bonded}$ = 3140 cm^{-1}. IR (CH_2Cl_2) : $\upsilon_{N\text{-}H\ free}$ = 3275 and $\upsilon_{N\text{-}H\ bonded}$ = 3150 cm^{-1}. IR (KBr) : 3175 cm^{-1}. Mass spectrum m/z (%) : M^+ = 232 (22) ; 199 (100). HRMS : calc. for $C_8H_{17}N_4PS$: 232.0912, found : 232.0909. Anal. calc. for $C_8H_{17}N_4PS$: C, 41.38 ; H,7.32 ; N, 24.13 ; found : C, 41.40 ; H, 7.43 ; N, 23.78.

- **General procedure for N- and S-alkylation (10c excluded) :** to a mixture of **5** (1 mmol) in THF (30 mL), after cooling at -30°C, n-butyllitium (1 mmol) was added and allowed to react for 20 min. The alkylating reagent (1 mmol) was added and the mixture and stirred at room temperature for about a night. The solvent was removed under reduced pressure and the residue solubilized with CH_2Cl_2. After filtration and evaporation of solvent, **9** and **10** were obtained.

- **Cyclen(benzylthio)phosphorane 9a :** 90 % yield, mp 74°C. ^{31}P NMR ($CDCl_3$) : -18.83 ppm. ^{13}C NMR ($CDCl_3$) : 37.57 (d, S-$\underline{C}H_2$, J_{PC} = 4.8 Hz), 44.20 (d, 8 N-$\underline{C}H_2$, J_{PC} = 9.2 Hz), 125.82 (1C, Φ), 127.81 (2C, Φ), 128.32 (2C, Φ), 141.76 ppm (d, 1C Φ, J_{PC} = 2.7 Hz). ^{1}H NMR ($CDCl_3$) : 2.65-2.82 (16 H), 3.82 (d, S-CH_2, $^{3}J_{PH}$ = 13.5 Hz), 7.12-7.37 ppm (5H, Φ).

- **Cyclen(methylthio)phosphorane 9b :** 90 % yield, mp 62-65°C[12]. ^{31}P NMR ($CDCl_3$) : -19.55 ppm. ^{13}C NMR ($CDCl_3$) : 16.30 (d, S-$\underline{C}H_3$, J_{PC} = 5 Hz), 44.03 ppm (d, 8 N-$\underline{C}H_2$, J_{PC} = 9.3 Hz). ^{1}H NMR ($CDCl_3$) : 2.05 (d, S-CH_3, $^{3}J_{PH}$ = 12.7 Hz), 2.85 (m, 8 H), 3.00 ppm (m, 8 H).

- **Cyclen(n-propylthio)phosphorane 9c :** 97 % yield, oil. ^{31}P NMR ($CDCl_3$) : -19.1 ppm. ^{13}C NMR ($CDCl_3$) : 13.67 ($\underline{C}H_3$), 25.41 (d, S-$CH_2\underline{C}H_2CH_3$, J_{PC} = 4.3 Hz), 34.97 (d, S-$\underline{C}H_2$, J_{PC} = 5.2 Hz), 44.34 ppm (d, 8 N-$\underline{C}H_2$, J_{PC} = 9.2 Hz). ^1H NMR ($CDCl_3$) : 0.93 (t, CH_3, $^3J_{HH}$ = 7.4 Hz), 1.48 (m, $C\underline{H}_2CH_3$), 2.54 (m, S-CH_2), 3.82 (m, 8H), 3.95 ppm (m, 8H).

- **Biscyclen(1,2-benzenedimethylthio)phosphorane 9d :** 98 % yield, mp 157°C. ^{31}P NMR ($CDCl_3$) : -18.77 ppm. ^{13}C NMR ($CDCl_3$) : 35.36 (d, 2 S-$\underline{C}$H2, J_{PC} = 4.7 Hz), 44.30 (d, 16 N-$\underline{C}H_2$, J_{PC} = 9.2 Hz), 126.17 (2C, Φ), 129.55 (2C, Φ), 138.99 ppm (d, 2C Φ, J_{PC} = 4.3 Hz). ^1H NMR ($CDCl_3$) : 2.70-3.15 (32H), 4.00 (d, 2 S-CH_2, $^3J_{PH}$ = 10.4 Hz), 7.09 (m, 4H, Φ), 7.23 ppm (m, 4H, Φ).

- **Biscyclen(1,3-benzenedimethylthio)phosphorane 9e :** 97 % yield, mp 174°C. ^{31}P NMR ($CDCl_3$) : -18.74 ppm. ^{13}C NMR ($CDCl_3$) : 37.53 (d, 2 S-$\underline{C}$H2, J_{PC} = 4.8 Hz), 44.24 (d, 16 N-$\underline{C}H_2$, J_{PC} = 9.3 Hz), 126.13 (2 C, Φ), 127.57 (1 C, Φ), 128.65 (1 C, Φ), 141.39 ppm (d, 2 C Φ, J_{PC} = 3.3 Hz). ^1H NMR ($CDCl_3$) : 2.70-3.00 (32H), 3.79 (d, 2 S-CH_2, $^3J_{PH}$ = 12.8 Hz), 7.09-7.21 (m, 6H, Φ), 7.26 ppm (m, 2H, Φ).

- **Biscyclen(1,4-benzenedimethylthio)phosphorane 9f :** 98 % yield, mp 192°C. ^{31}P NMR ($CDCl_3$) : -18.71 ppm. ^{13}C NMR ($CDCl_3$) : 37.32 (d, S-$\underline{C}H_2$ J_{PC} = 4.7 Hz), 44.11 (d, 16 N-$\underline{C}H_2$, J_{PC} = 9.2 Hz), 127.95 (4 C, Φ), 139.41(2 C, Φ). ^1H NMR ($CDCl_3$) : 2.70-3.00 (32H), 3.78 (d, 2 S-CH_2, $^3J_{PH}$ = 13.5 Hz), 7.17 ppm (s, 8H, Φ).

- **N-benzoylcyclenphosphine sulfide 10a :** 98 % yield, mp 252°C. ^{31}P NMR ($CDCl_3$) : 84.22 ppm. ^{13}C NMR ($CDCl_3$) : 44.02 (d, 1 N-$\underline{C}H_2$, J_{PC} = 4.5 Hz), 46.95 (d, 1 N-$\underline{C}H_2$, J_{PC} = 4.7 Hz), 50.60 (1 N-$\underline{C}H_2$), 50.86 (d, 2 N-$\underline{C}H_2$, J_{PC} = 3.7Hz), 50.99 (d, 1 N-$\underline{C}H_2$, J_{PC} = 16.6 Hz), 51.46 (d, 1 N-$\underline{C}H_2$, J_{PC} = 15.9 Hz), 51.85 (1 N-$\underline{C}H_2$), 125.79 (2 C, Φ), 128.25 (2 C, Φ), 128.73 (1 C, Φ), 137.15 (1 C, Φ), 172.36 ppm (C=O). ^1H NMR ($CDCl_3$) : 2.50-4.30 (16H), 7.35-7.42(3H, Φ), 7.55-7.60 ppm (2H, Φ). IR (CH_2Cl_2) : $\upsilon_{C=O}$ =1641 cm^{-1}.

- **N-propanoylcyclenphosphine sulfide 10b :** 97 % yield, mp 213°C. ^{31}P NMR ($CDCl_3$) : 83.92 ppm. ^{13}C NMR ($CDCl_3$) : 9.18 (CH_3), 26.61 ($\underline{C}H_2CH_3$), 44.86 (d, 1 N-$\underline{C}H_2$, J_{PC} = 4.6 Hz), 46.60 (d, 1 N-$\underline{C}H_2$, J_{PC} = 4.2 Hz), 50.60 (d, 1 N-$\underline{C}H_2$, J_{PC} = 3.4 Hz), 50.81 (d, 1 N-$\underline{C}H_2$, J_{PC} = 2.0 Hz), 50.85 (d, 1 N-$\underline{C}H_2$, J_{PC} = 3.4 Hz), 51.12 (d, 1 N-$\underline{C}H_2$, J_{PC} = 18.2 Hz), 51.41 (1 N-$\underline{C}H_2$), 51.50 (d, 1 N-$\underline{C}H_2$, J_{PC} = 8.33 Hz), 174.77 ppm (C=O). ^1H NMR ($CDCl_3$) : 1.87 (t, CH_3, $^3J_{HH}$ = 7.4 Hz), 2.3-4.2 ppm (18H). IR (CH_2Cl_2) : $\upsilon_{C=O}$ = 1645 cm^{-1}.

- **N-(2-cyanoethyl)cyclenphosphine sulfide 10c** : To a solution of **5** (1 mmol) in EtOH (30 mL) an excess of acrylonitrile (2 mmol) was added and the mixture was stirred overnight at 60°C. After evaporation of the mixture, **10c** was obtained. 93 % yield, mp 208°C. ^{31}P NMR ($CDCl_3$) : 79.59 ppm. ^{13}C NMR ($CDCl_3$) : 12.56 ($\underline{C}H_2CN$), 44.77 (2 N-$\underline{C}H_2$), 45.90 (1 N-$\underline{C}H_2$), 48.92 (d, 2 N-$\underline{C}H_2$, J_{PC} = 3.5 Hz), 50.10 (d, 2 N-$\underline{C}H_2$, J_{PC} = 14.4 Hz), 50.68 (2 N-$\underline{C}H_2$), 119.02 ppm (CN). ^1H NMR ($CDCl_3$) : 2.5-3.5 (20H).

- **anion 11 :** to a mixture of **5** (1 mmol) in THF (30 mL), after cooling at -30°C, n-butyllithium (1 mmol) was added and allowed to react for 20 minutes. The solvent is removed under reduced pressure. ^{31}P NMR (CD_2Cl_2) : -51 ppm. ^{13}C NMR (CD_2Cl_2) : 44.77 ppm (d, 8 N-$\underline{C}H_2$, J_{PC} = 9.2Hz).

- **Reduction of 10a, 10b and hydrolysis :** (typical procedure for reduction of amides) : the compound was dissolved in THF (100 mL), a solution of $BH_3.SMe_2$ (5/3 equivalents) was then added, and the mixture refluxed overnight. After cooling, the excess of $BH_3.SMe_2$ was destroyed by

slow addition of MeOH, and the solution evapored to leave a white solid. This was taken up in 10% of aqueous HCl (100 mL) and refluxed for 12 hours (the hydrolysis of the P=S function occurs simultaneously). After cooling, the pH was raised to 14 with NaOH pellets and the product extracted with CH_2Cl_2 (3 x 25 mL). After drying ($MgSO_4$) and evaporation of solvent, pure mono N-alkylated tetraamine was isolated. The end products were described elsewhere[21].

ACKNOWLEDGEMENTS

The Region Bretagne is gratefully acknowledged for financial support, SIMAFEX (17230 Marans, France) for generous gifts of cyclen trisulfate and Dr. R. Pichon and N. Kervarec for recording NMR spectra.

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(*Received in Belgium* 19 *June* 1995; *accepted* 26 *December* 1995)