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SYNTHESIS OF NOVEL CROWN DERIVATIVES INCORPORATING A DIAMINOPHOSPHINE GROUP IN A POLYETHER MACROCYCLE

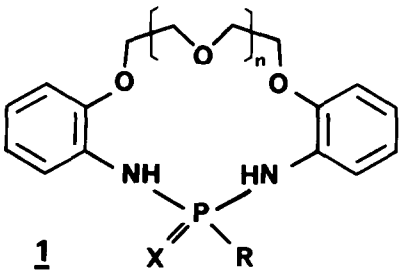
Jean Pierre DUTASTA* and Pascal SIMON

Laboratoire L.E.D.S.S., UA C.N.R.S. n° 332, Université Scientifique et Médicale de Grenoble, BP 68, F-38402 Saint Martin d'Heres Cedex - France

Abstract: *The efficient synthesis of 17- to 21-membered ring phosphorus compounds is described. The derivatives incorporate a diaminophosphine group in a polyether macrocycle.*

Macrocycles possessing phosphorus have been synthesized as phosphine oxides[1,2,4], phosphines[2-5], phosphonium salts[4-6], phosphites[7], phosphates[8], phosphonates[9,10] and phosphoranes[11]. Various metallic complexes have been obtained from these ligands. The importance of these molecules as phosphorus analogues of crown ethers, their potential catalytic activity and ion-carrier properties, make their development desirable. Hexamethylphosphoramide (HMPA) and its derivatives are well known complexing agents for organic and inorganic compounds. The design of phosphorus macrocycles incorporating HMPA units or aminophosphine groups may give rise to powerful new complexing agents with high selectivity and stability. We therefore undertook the synthesis of several such macrocyclic phosphorus compounds and we now report our findings.

The derivatives **1** and **2**, which incorporate one diaminophosphine-sulfide unit, are particularly attractive as both a binding subunit and a building block for the construction of preorganized systems.[12]



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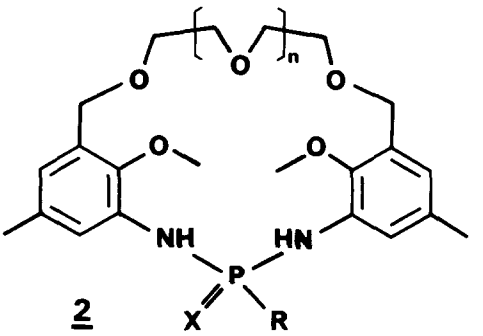

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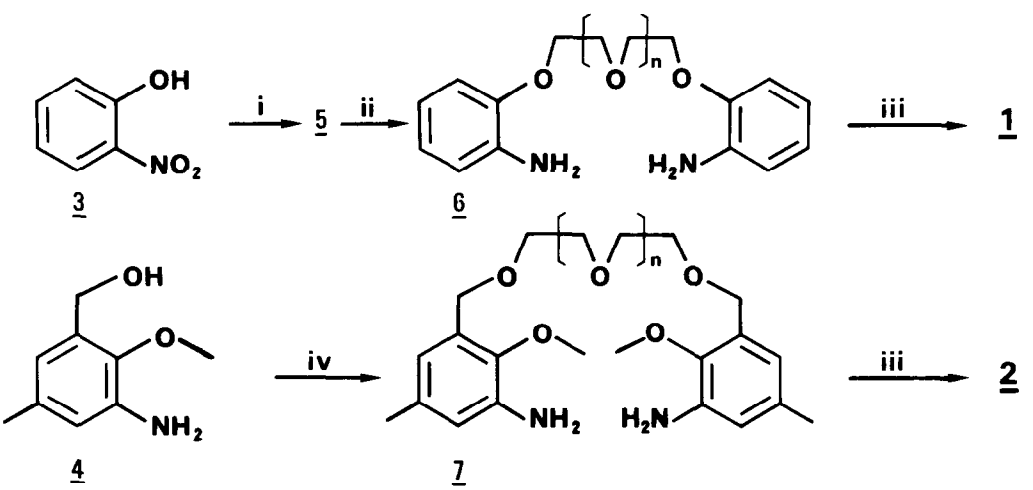
The synthetic route is outlined in the scheme and begins with 2-nitrophenol **3** or 2-methoxy-3-amino-5-methyl benzyl alcohol **4**.[13] Compounds **5a** (n = 2) and **5b** (n = 3) are prepared from **3** by reaction with triethylene glycol ditosylate (or triethylene glycol dichloride) and tetraethylene glycol ditosylate through known procedures.[14] Reduction of **5a** and **5b** with hydrazine-Pd-C in ethanol produces the corresponding dianiline derivatives **6a** (n = 2; 92%) and **6b** (n = 3; 81%). Compounds **7a** (n = 1) and **7b** (n = 2) are prepared by the addition of **4** to a suspension of NaH and diethylene glycol ditosylate or triethylene glycol ditosylate in anhydrous tetrahydrofuran. After the reaction, the THF is evaporated and the mixture is partitioned between $CHCl_3$ and water. **7a** and **7b** are recovered from the organic phase as oils (83% and 85%, respectively), and are used without further purification.

Compounds **6a** and **6b** are treated with bis-(dimethylamino)-phenyl phosphine[15] in refluxing toluene to yield the three-coordinated derivatives (**1**, R = Ph, X = lone pair, n = 2 and 3). At this stage the P^{III} species are not isolated but converted to the P^{IV} analogues by reaction with sulfur to give **1a** (n = 2, R = Ph, X = S, $\delta^{31}P$ = 54.8 ppm) and **1b** (n = 3, R = Ph, X = S, $\delta^{31}P$ = 55.6 ppm). Similarly, treatment of **7a** and **7b** with bis-(dimethylamino)-phenyl phosphine in refluxing toluene followed by addition of sulfur yields the macrocyclic diaminophosphines **2a** (n = 1, R = Ph, X = S, $\delta^{31}P$ = 52.3 ppm) and **2b** (n = 2, R = Ph, X = S, $\delta^{31}P$ = 57.2 ppm).



i) TsO(CH$_2$CH$_2$O)$_n$CH$_2$CH$_2$OTs/K_2CO_3/DMF/reflux. **ii)** NH_2NH_2/Pd-C/EtOH/reflux.
iii) $C_6H_5P(N(CH_3)_2)_2$/toluene/reflux. **iv)** TsO(CH$_2$CH$_2$O)$_n$CH$_2$CH$_2$OTs/NaH/THF/45°C.

Although the macrocyclization reactions are not carried out under high dilution conditions (3 10^{-2}M), compounds **1** and **2** are obtained in fairly good yields. **1** (X = lone pair) is the major compound formed during the macrocyclization reaction (n = 2, ~80% ; n = 3, ~70% ; based on the ^{31}P NMR spectra of the reaction mixtures). The conversion with sulfur is nearly quantitative and **1a** (mp 165°C) and **1b** (mp 146°C) are obtained in overall isolated yields of 78% and 63%, respectively. Compounds **2a** and **2b** are readily separated from the crude mixtures by column chromatography on silica to yield the

pure materials (**2a**, 10%, mp 150°C; **2b**, 20%, mp 139°C; yields not optimized).

In the course of the reaction of **6b** with bis-(dimethylamino)-phenyl phosphine, oligomeric materials are formed as evidenced by size exclusion chromatography (SEC) and ^{31}P NMR. However, the heating of the mixture under reflux in dilute toluene solution results in partial depolymerization and gives rise principally to the monomeric macrocycle (**1**, n = 3, R = Ph, X = lone pair) in addition to minor amounts of higher molecular weight compounds. The procedure, of obvious synthetic interest, is closely related to that reported for 1,3,2-dioxaphospha derivatives.[9] This depolymerization process has also been found to occur with similar 1,3,2-diazaphospha compounds.

The macrocycles **1a–b** and **2a–b** have been characterized by elemental analysis, mass spectroscopy, and ^{1}H and ^{13}C NMR.[16] **1a–b** and **2a–b** display the anticipated spectral characteristics. The ^{1}H NMR spectra of **2a** and **2b** in $CDCl_3$ exhibit a well-defined AB quartet for the benzylic protons at δ = 4.31 and 4.40 ppm (J = 11.7 Hz) and δ = 4.28 and 4.51 ppm (J = 10.6 Hz), respectively.

Thus, starting from **6** and **7**, crown derivatives that have an intraannular diaminophosphine unit can be obtained. Various chain lengths can also be used and therefore a family of macrocyclic diaminophosphines of various sizes can be generated. In addition, oxide derivatives can readily be prepared: e.g. **1c** (n = 2, R = Ph, X = O) has been obtained both from the three-coordinated parent compound by reaction with N_2O_4 and from **1b** by treatment with m-chloroperbenzoic acid ($\delta^{31}P$ = 10.7 ppm). Furthermore, the method has been applied to other phosphorus reagent: e.g. HMPT (Hexamethylphosphorus triamide) on successive treatment with **6a** (n = 2) and sulfur yields the thiophosphoramide derivative **1d** (n = 2, R = $N(CH_3)_2$, X = S, $\delta^{31}P$ = 53.7 ppm) .

In conclusion, the synthetic route described herein has the following advantages : (i) yields are high and compounds are easily recovered and purified from the crude mixtures ; (ii) the P^{III} and sulfurized or oxidized P^{IV} derivatives can readily be obtained in all cases, thus opening routes to new families of ligands; a variety of inorganic and organic ions may form stable complexes with these molecules by binding to the polyether in the macrocycle and interacting with the phosphorus group ; (iii) finally, compounds **1** and **2** are potentially key intermediates for the synthesis of rigid preorganized systems : substitution on the phosphorus-amido groups may enhance steric hindrance and lead to enforced cavities.

The study of the complexation of cationic entities with these mixed phosphorus-ether ligands and the synthesis of more rigid molecules are presently in progress.

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(16) ^{1}H and ^{13}C NMR data (δ in ppm relative to TMS, J in Hertz).

Compound (**1a**) ^{1}H-NMR ($CDCl_3$) : 3.67-3.83 (m, 8H, OCH_2); 4.10-4.21 (m, 4H, OCH_2); 6.18 (br d, J_{PH} = 4.8, 2H, NH) ; 6.71-6.88 (m, 6H, arom H); 7.26-7.50 (m, 5H, arom H); 8.10-8.20 (m, 2H, arom H). ^{13}C-NMR ($CDCl_3$) : 69.45, 69.52, 70.72 (OCH_2) ; 113.87, 119.14 (J_{PC} = 3.9), 121.82, 121.85, 131.27 (J_{PC} = 1.6), 148.27 (J_{PC} = 7.9) (arom C); 128.37 (J_{PC} = 14.4), 131.72 (J_{PC} = 3.2), 131.85 (J_{PC} = 12.2), 135.69 (J_{PC} = 123.4) (P-arom C).

Compound (**1b**) ^{1}H-NMR ($CDCl_3$) : 3.50-3.84 (m, 12H, OCH_2); 4.04-4.21 (m, 4H, OCH_2); 6.42 (br s, 2H, NH); 6.71-6.92 (m, 6H, arom H); 7.32-7.56 (m, 5H, arom H); 8.06-8.18 (m, 2H, arom H) ^{13}C-NMR ($CDCl_3$) : 68.43, 69.56, 70.43, 71.12 (OCH_2); 112.15, 118.91 (J_{PC} = 3.9), 121.24, 121.47, 130.54 (J_{PC} = 2.1), 148.11 (J_{PC} = 8.1) (arom C); 128.27 (J_{PC} = 14.2), 131.61 (J_{PC} = 3.1), 131.82 (J_{PC} = 12.3), 135.49 (J_{PC} = 120.8) (P-arom C).

Compound (**2a**) ^{1}H-NMR ($CDCl_3$) : 2.09 (s, 6H, CH_3); 3.25-3.51 (m, 8H, OCH_2); 3.38 (s, 6H, OCH_3); 4.31 and 4.40 (AB d, J = 11.7, 4H, CH_2-arom); 5.97 (d, J_{PH} = 6.2, 2H, NH); 6.63 (s, 2H, arom H); 7.23 (s, 2H, arom H); 7.45-8.05 (m, 5H, P-arom H). ^{13}C-NMR ($CDCl_3$) : 21.01 (CH_3), 61.93 (OCH_3), 68.04, 68.43, 70.10 (OCH_2); 120.29 (J_{PC} = 3.6), 125.48, 130.42, 133.28, 133.31 (J_{PC} = 3.6), 146.96 (J_{PC} = 7.0) (arom C); 129.24 (J_{PC} = 14.2), 129.98 (J_{PC} = 11.2), 132.03 (J_{PC} = 3.2), 136.46 (J_{PC} = 134.5) (P-arom C).

Compound (**2b**) ^{1}H-NMR ($CDCl_3$) : 1.99 (s, 6H, CH_3); 3.47-3.56 (m, 12H, OCH_2); 3.68 (s, 6H, OCH_3); 4.28 and 4.51 (AB d, J = 10.6, 4H, CH_2-arom); 5.77 (d, J = 6.2, 2H, NH); 6.69 (s, 4H, arom H); 7.32-7.82 (m, 5H, P-arom H). ^{13}C-NMR ($CDCl_3$) : 20.87 (CH_3); 62.42 (OCH_3); 68.19, 69.69, 70.65, 70.82 (OCH_2); 122.53 (J_{PC} = 3); 126.03, 130.65, 132.60, 133.71, 148.04 (J_{PC} = 7) (arom C); 128.55 (J_{PC} = 14), 131.14 (J_{PC} = 11), 131.91, 134.74 (J_{PC} = 126) (P-arom C).

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