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Design, synthesis and characterization of novel heterocyclic compound [3,3,0]

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N,N-Bis(2-chloroethyl)-N",N"-diarylphosphorotriamidate was prepared by reaction of (1) with anilines in refluxing THF. These phosphorotriamidate reacted with one equivalent of potassium tert-butoxide at 0 ºC to give the diazaphospholidine, and with two equivalents of potassium tert-butoxide at elevated temperatures to yield a novel hetro[3,3,0]bicyclic ring system with interesting structural features. Bis(2-phenylaminoethyl)amine hydrochloride (3) is readily prepared by reaction of bis(2-chloroethyl)amine hydrochloride and four molar equivalents of aniline in methanol solvent at low temperature. The crude is purified with vacuum distillation. From the reaction of bis(2-phenylaminoethyl)amine and $POCl_3$, the bicyclic compound (4) was only obtained. Reactions proceed in high yield, under mild conditions. The structures of prepared compounds were confirmed by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR spectroscopy and X-ray crystallography.

Keywords: phosphorotriamidate –bicyclic ring- alkylating -heterocyclic

INTRODUCTION

Chemistry synthetic organophosphorus connections have not only significant effect on the development of modern theoretical organic chemistry, but also is of considerable practical interest [1,2,3]. In order to obtain the most effective drugs were Synthesizing, and explore the many new organophosphorus compounds [4, 5]. Research in this area has led to the discovery of new methods the synthesis of biologically active compounds for use in a variety of biochemical processes that occurring in living organisms [6]. In 1948 Gomori [7] reported that the activity of phosphoramides enzymes was localized in certain tumors. Based on this report, Friedman and Seligman [8, 9] synthesized several resonances –stabilized N-phosphorylated nitrogen mustards. Similarly, Rapp and Kuzmenko *et al*.[10-13] have synthesized several derivatives of N-phosphorylated nitrogen mustards using the method of Friedman and Seligman [8, 9] sometimes via a different route. The antitumor activities of these compounds were investigated and it is reported that some of them have shown activity [14, 15]. Recently, ^{15}N labeled and ^{17}O labeled phosphoramide mustards have been synthesized [16, 17]. Examination of the spectra has revealed that under acidic conditions (pH 1-4.9) phosphoramide mustard exists as the zwitterion, a piece of useful information certain to contribute to drug design. As already noted, cyclophosphamide was prepared as a "pro-drug" that would release bis(2-chloroethyl)amine in tumor cells following hydrolysis of the exocyclic P-N bond. Although it is now understood that the metabolic transformation of cyclophosphamide in vivo is an oxidative process, still, the in vitro hydrolytic fate of cyclophosphamide has been of interest, [18] to the extent that its understanding helps explain the fate of the drug in vivo. Friedman and co-workers [19-21] have examined this problem in some detail and, consistent with experimental results, have proposed a pathway for the spontaneous hydrolysis of cyclophosphamide. These results suggest that in spontaneous hydrolysis of cyclophosphamide, the first step involves intramolecular N-alkylation which is then followed by a series of P-N and P-O bond cleavages. Zon and co-workers [22-24] have re-investigated the hydrolysis of cyclophosphamide employing appropriate deuterium labels and high-resolution NMR spectroscopy and have obtained results. Subsequently, the scope of this metal hydride-mediated cyclization reaction as a route to interesting heterocyclic ring systems was briefly explored [25].Following the synthesis of phosphorylated mustards by Friedman and Seligman, [8] and subsequent to the elucidation of the metabolism of cyclophosphamide which has highlighted the central role played by phosphoramide mustard in its cytotoxicity, a good number of phosphoramide mustard derivatives have been synthesized especially by Rapp and co-workers [10-13]. Subsequently, the same authors have reported the synthesis of the diamide derivatives via a phosphoramidochloridate prepared by reacting aryl or alkyl N,N-bis(2-chloroethyl)phosphoramidochloridate with amino acids [26]. The antitumor activities of these compounds were investigated and it is reported that some of them have shown activity.

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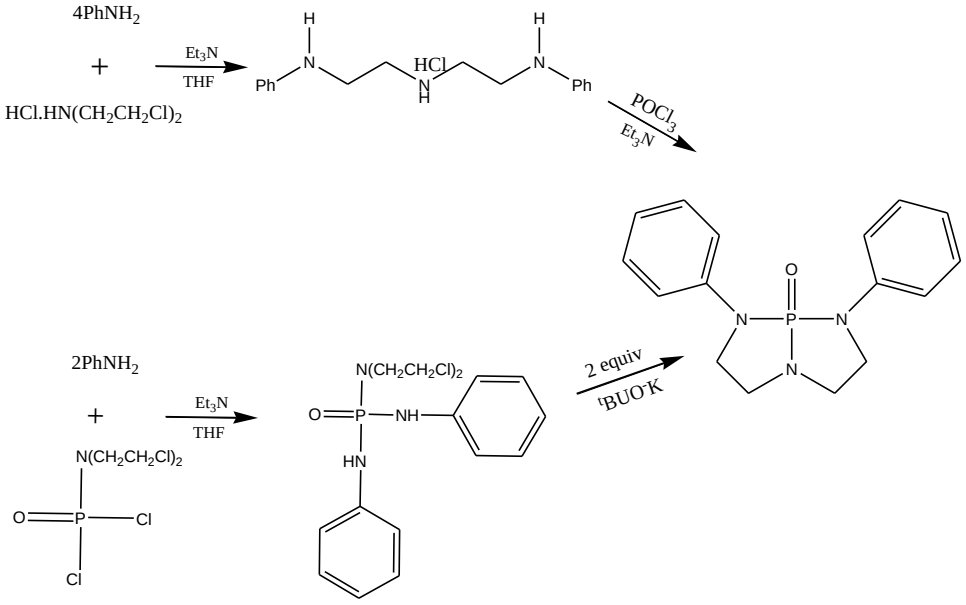
This work reports the synthesis of 2, 8-diphenyl-2, 5, 8-triaza-1-phosphabicyclo [3.3.0] octane 1-oxide from two ways. These cyclization reactions as a route to interesting heterocyclic ring systems were briefly explored. Reaction pathway for the preparation of target compound in Scheme 1.



Scheme1. Reaction path for the preparation of target compounds **2**.

MATERIALS AND METHODS

^{31}P NMR spectra were recorded on a Varian DPX300 spectrometer operating at 101.249 MHz and shifts are reported in units of d relative to 85 % phosphoric acid as external standard, positive shifts are downfield. ^{13}C NMR spectra were recorded on a Varian DPX300 spectrometer operating at 62.902 MHz and shifts are reported in units of d relative to TMS. Both ^{13}C and ^{31}P NMR spectra were proton noise decoupled and all signals were singlets unless otherwise stated. ^{1}H NMR spectra were recorded on a Varian DPX300 spectrometer operating at 250.132 MHz and are reported in units of d relative to TMS. All NMR spectra were recorded in $CDCl_3$ and TMS as internal standard or 85 % H_3PO_4 as external standard unless otherwise stated and all coupling constants are reported in Hz. EI-MS were recorded on a VG7070H spectrometer. All experiments involving water sensitive reagents were carried out under dry conditions. Where needed, anhydrous solvents and reagents were obtained in the following ways: Et_3N, Et_2O, hexane, and CH_2Cl_2, were refluxed over CaH_2 for several hours and distilled. All but Et_3N were further dried over activated 4 Å molecular sieves. All alcohols were distilled onto activated 4 Å molecular sieves. The reactions were monitored by TLC and visualized with UV light followed by development using *n*-hexane and ethyl acetate 7:3 (v/v) and Et_2O: hexane (3:1) as an eluent. The X-ray diffraction analysis was carried out on the device Siemens PZ/PC, dispersion of X-rays under small corners. When performing experimental works used books and the monograph [27- 29].

EXPERIMENTAL

Synthesis of N,N'-diphenyl-N'',N''-bis(2-chloroetheyl)-phosphorortiamidate (1):

To a refluxing mixture of aniline (7.73 g, 0.0830 mol) and triethylamine (8.18 g, 0.0808 mol) in THF (10 mL) was added drop wise over 20 min a solution of N,N-bis(2-chloroethyl) phosphoramidodichloridate (61) (10.5 g, 0.0404 mol) in THF (40 mL). The reaction was allowed to run for 14 h at which time ^{31}P NMR showed it to be complere. It also showed the presence of a side product, δ:-3.2, in 6% yield. This side product was not isolated in this particular case but has been identified as a phosphinimine arising from loss of HCl from the intermediate in the reaction . HCl was added (200 ml) and the mixture was extracted with methylene chloride (4×200 mL). After neutralization of excess acide (saturated $NaHCO_3$), the organic phase was washed with brine the wash was neutral to litmus, deide (Na_2SO_4), and the filtrate concentrated in vacuo. It was subsequently subjected to a high vacuum overnight when it crystallized as a white solid. The crude crystals were recrystallized from toluene/acetone to afford the title compound, 12.77 g (85%); m.p. 189.5-190.0 ºC (literature10 16%, 185-186 ºC).

^{1}H NMR ($CDCl_3$) δ: 3.36-3.41 (q, CH_2, 4H), 3.54-3.58 (q, CH_2, 4H), 6.83-6.87 (m, Ar, 2H), 7.14-7.22 (m, Ar, 8H), 7.65-7.68 (d, N-H, 2H). ^{13}C NMR ($CDCl_3$) δ: 42.15 (s, C1), 48.86 (d, $^{3}J_{P-C}$ = 4.5 Hz, C2), 117.53 (d, $^{3}J_{P-C}$ = 6.3 Hz, C3), 120.26 (s, C5), 128.70 (s, C4), 141.98 (s, C8). ^{31}P NMR ($CDCl_3$) δ: 4.79.

Synthesis of 2, 8-diaryl-2, 5, 8-triaza-1-phosphabicyclo [3.3.0] octane 1-oxide (2):

To a refluxing suspension of N,N'-diphenyl-N",N"-bis(2-chloroethyl)phosphorotriamidate (1) (3.92 g, 0.011 mol, 1 mol, 1 mol equiv.) in dry toluene (30 mL) was added potassium tret-butoxide (22.0 mL, 0.022 mol, 2 equiv). There was an instantaneous reaction; the reaction mixture first turning clear and then trbid. The reaction was allowed to continue for 1 h and cooled. Brine (200 mL) was added and the mixture was extracted with methylene chloride (2×200 mL). the organic layer was washed once with brine (100 mL), dried (Na_2SO_4), and filtered. Removal of solvent in vacuo gave the title compound as a white, solid residue, 2.95 g (94%). The solide was future purified by recrystallization from hexane/toluene, 2.68 g (85%); mp 146.5-147.0 ºC.

^{1}H NMR ($CDCl_3$) δ: 3.06-3.16 (m, CH^{a}, $CH^{a'}$, 2H), 3.53-3.62 (m, CH^{b}, $CH^{b'}$, 2H), 3.63-3.72 (m, CH^{c}, $CH^{c'}$, 2H), 3.80-3.88 (m, CH^{d}, $CH^{d'}$, 2H), 6.93- 6.97 (m, Ar, 2H), 7.16-7.22 (m, Ar, 8H). ^{13}C NMR ($CDCl_3$) δ: 47.52 (d, $^{2}J_{P-C}$ = 7.1 Hz, CH_2), 48.55 (d, $^{2}J_{P-C}$ = 20.0 Hz, CH_2), 118.30 (d, $^{3}J_{P-C}$ = 3.6 Hz, C5), 121.60 (s, C7), 128.52 (s, C6), 141.60 (d, $^{2}J_{P-C}$ = 5.4 Hz, C10). ^{31}P NMR ($CDCl_3$) δ: 33.16; Anal. Calcd for $C_{16}H_{18}N_3OP$: C, 64.21; H, 6.06; N, 14.04. Found: C, 64.12; H, 6.11; N, 14.04.

Synthesis of Bis(2-phenylaminoethyl)amine Hydrochloride (3):

The title compound was prepared according to a literature procedure [11]. Thus, aniline (21.5 g, 0.231 mol) and N, N-bis(2-chloroethyl)amine hydrochloride (61D)(10.1 g, 0.0570 mol) were placed in a round- bottom flask with methanol (56 mL). A reflux condenser was attached and the reaction was refluxed for 16 hours at which the product appeared as silvery-white flakes insoluble in the reaction mixture. The reaction mixture was cooled and the precipitated solid was collected by suction filtration. It was washed several times with cold methanol and dried in vacuum to give the title compound as white flakes, 3.59 g (25%), mp 235.0-237.5 ºC (dec) (Lit.[11] 237 oC). ^{1}H NMR (DMSO-d6) δ: 3.10 (s, CH_2, 4H), 3.39 (s, CH_2, 4H), 5.95 (s, ArNH-, 2H), 6.56-6.65 (m, Ar, 6H), 7.08-7.12 (m, Ar, 4H), 9.29 (s, $(-CH_2)_2$NH.HCl, 2H). ^{13}C NMR (DMSO-d6) δ: 39.10 (s, CH_2), 45.85 (s, CH_2), 112.24 (s, Cpara), 116.33 (s, Cortho), 128.89 (s, Cmeta), 147.91 (s, Cipso).

Synthesis of 2, 8-diphenyl-2, 5, 8-triaza-1-phosphabicyclo [3.3.0] octane 1-oxide (4):

Phosphorus oxychloride (1.35 g, 8.77 mmol) in toluene (10 mL) was added over 45 min to a refluxing suspension of N, N-bis(2-phenylaminoethyl)amine hydrochloride (1) (2.58 g, 8.86 mmol.) and triethylamine (3.72 g, 0.0368 mol) in toluene (90 mL). Reflux was maintained until all of the hydrochloride (silver flakes) had disappeared. Water (200 mL) was added and the mixture was extracted with methylene chloride (600 mL). The combined methylene chloride phase was washed with water (150 mL), dried (Na_2SO_4), and filtered. The solvent was removed from the filtrate under vacuum to give a brown semi-solid crude. Examination of the crude reaction mixture with ^{31}P NMR showed there were many products formed in addition to the expected compound. The residue was dissolved in methylene chloride, stirred with silica gel to remove coloring matter, and filtered. The filtrate was concentrated to a pale yellow semi-solid which was dissolved in hexane/toluene and set aside. Overnight, white crystals precipitated from solution and were collected, 0.0775 g. The mother liquor was concentrated, again diluted and set aside, and from it, more crystals were isolated, 0.0604 g, for a combined yield of 1.138 g, (74%); mp 146.5-147.0 ºC. ^{1}H NMR ($CDCl_3$) δ: 3.06-3.16 (m, CH^{a}, $CH^{a'}$, 2H), 3.53-3.62 (m, CH^{b}, $CH^{b'}$, 2H), 3.63-3.72 (m, CH^{c}, $CH^{c'}$, 2H), 3.80-3.88 (m, CH^{d}, $CH^{d'}$, 2H), 6.93- 6.97 (m, Ar, 2H), 7.16-7.22 (m, Ar, 8H). ^{13}C NMR ($CDCl_3$) δ: 47.52 (d, $^{2}J_{P-C}$ = 7.1 Hz, CH_2), 48.55 (d, $^{2}J_{P-C}$ = 20.0 Hz, CH_2), 118.30 (d, $^{3}J_{P-C}$ =3.6 Hz, C5), 121.60 (s, C7), 128.52 (s, C6), 141.60 (d, $^{2}J_{P-C}$ = 5.4 Hz, C10). ^{31}P NMR ($CDCl_3$) δ: 33.16; Anal. Calcd for $C_{16}H_{18}N_3OP$: C, 64.21; H, 6.06; N, 14.04. Found: C, 64.12; H, 6.11; N, 14.04.

RESULTS AND DISCUSSION

Characterization of 2, 8-diphenyl-2, 5, 8-triaza-1-phosphabicyclo [3.3.0] octane 1-oxide

As noted earlier, this compound was prepared in 74% isolated yield. Examination of the ^{1}H NMR spectrum, of the compound showed that in the region corresponding to aromatic hydrogens, there were two sets of multiplets (δ= 7.16 – 7.22, 8H; δ= 6.93 – 6.97, 2H). The multiplet appearing downfield corresponds to the ortho-and meta-hydrogens, while the multiplet appearing upfield is

due to the para hydrogens. In the ^{13}C NMR spectrum, there were only four lines for the phenyl rings. These NMR data indicate that the two phenyl rings in (2) are equivalent. This equivalence of the phenyl rings suggests a symmetrical structure for the compound. In the aliphatic region of the

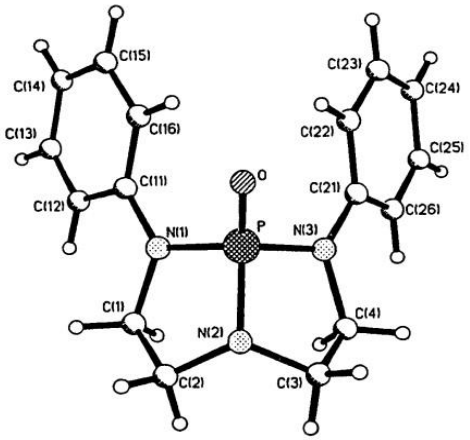


Fig 1. X-ray crystal structure of 2, 8-diphenyl-2, 5, 8-triaza-1-phosphabicyclo [3.3.0] octane 1-oxide (2) in $CDCl_3$.

^1H NMR spectrum corresponding to the ring methylene hydrogens, there was extensive coupling indicating a folded structure of the two rings. This is supported by the ^{31}P NMR spectrum which shows a significant downfield shift of the resonance. The downfield shift is an indication that the anilino nitrogens are no longer making full electron contribution to the phosphourus atom, which would be the case in a rigid structure in which overlap of the orbitals is severely hindered. Because of the suggested symmetry of the compound, and the novelty of the ring system, it was further investigated in order to obtain more information about the structural characteristics.

An experimental dipole moment of (2) was measured in benzene solution at 30 ^oC and was found to be 5.61 D. The theoretical dipole moment of the compound was also calculated by AM 1 (Austin Method 1) semi – empirical method from two contributions: point – charge = 3.658 and sp hybrid = 1.826 D which give the total dipole moment of 5.48 D. This calculated dipole moment compares well with that (5.61) obtained experimentally. Considering that the experimental moment was determined in benzene solution whereas the calculation is for the gas phase, the closeness of the values indicates there is little solvent – solute interaction.

Stereochemistry and torsion angle

An interesting of the structure is that both phenyl groups are in endo positions with respect to the bicycle skeleton. In bicycle systems in general, exo substitution is less hindered (lower energy structure) than endo substitution; however, systems other than carbocyclic have not been extensively studied. A reasonable explanation for the phenyl positions follows. It can be noted from the improper torsion angles of 178.0o (167.5 cryst) and 179.8 (164.0 cryst) for N(1)-C(11)-C(1)-P and N(3)-C(21)-C(4)-P respectively that the N (1) and N(3) nitrogens are trigonal (sp2) since they are approximately coplanar with the attached atoms, C(1), C(11), P and C(24), P respectively whereas the bridgehead nitrogen, N(2) is sp3 hybridized, with the sp2 hybridization, the two unpaired electrons on N(1) and N(3) are in π orbitals oriented so as to delocalize these electrons into the respective phenyl rings. Evidence for electron donation into the para positions (C14 and C24) of the phenyl rings is from the upfield positions (at δ 6.93-6.97) of the hydrogens attached to C14 and C24 relative to the positions of the other eight phenyl hydrogens at δ 7.16-7.22.

Dipole moment study

The dipole moment is relatively large as compound with reported moments of other compounds containing the P=O group. Thus, values of 4.2 and 4.29 D in benzene solution at were reported for trimethylphosphine oxide ($Me_3P=O$), 4.34 to 4.53 D for triphenylphosphine oxide ($Ph_3P=O$) and 4.30 and 4.31 D for $(Me_2N)_3P=O$ (hexamethylphosphoric acid triamide) [10]. One possible explanation is that the bicyclization with the phosphorus atom in the bridgehead position creates strain at that position which results in greater polarization of the P=O bond with a consequential greater moment. The low values for the N(1)-P-N(2) and N(3)-P-N(2) bond angles of 98.8^o indicate this strain. The atomic charges of -1.089 at oxygen and 2.770 at phosphorus additionally reflect this polarization.

Molecular structure

Comparisons of the bond lengths and bond angles as determined from the solution dipole moment and single crystal structure measurements show that corresponding values are very close indicating the rigidity of the bicyclic skeletal structure. Slightly larger differences are present in the orientation of the phenyl rings with respect to the bicyclic skeleton. Excepting for differences

between the orientations of the two phenyl rings, there is a plane of symmetry through the phosphorus, oxygen, and bridgehead nitrogen (N_2) atoms for both structures – that from the crystal structure and from the solution dipole moment and calculated determinations. The methylene hydrogens on adjacent carbons are in approximate staggered positions. The H/H nonbonded interactions force both of the five – membered rings of the bicyclic skeleton into a puckered conformation similar to that in cyclopentane as shown by the X-ray crystal structure (figure 1).

Bond lengths

The relevant bond lengths are also in accord eith this interpretation thus, the sp2-sp2 N(1)-C(11) and N(3)-C(21) bond lengths to the phenyl rings of 1.401 (1.421 cryst) and 1.402 Å (1.391 cryst) respectively are significantly shorter than those of sp2 –sp3 character, N(1)-C(1) and N(3)-C(4) to the methylene carbons of 1.443 (1.461 cryst) and 1.444 Å (1.492 cryst) respectively. Note that the bond lengths from the bridgehead nitrogen to the methylene carbons of sp3 –sp3 character, N(2)-C92) and N(2)-C(3), of 1.440 Å are also relatively long. In addition, the bond distances from phosphorus to N(1) and N(3) of 1.619 Å are indicative of an sp2 - sp3 bond as compared with the longer P-N(2) sp3d –sp3 bond length of 1.657 Å. Inexplicably, all three bonds to phosphorus (N-1,N-2, and N-3) in the crystal state have about the same bond length of 1.66 Å. In any case, no significant π electron donation from nitrogen to phosphorus is evident. In fact any such donation, as Scheme A shows, would be a violation of Bredt's rule if this rule could be applied to heteroatoms instead of to carbon as usually discussed.

Angels between planes

If the angles between planes are considered, the angle between the phenyl ring (plane 1) and the relevant atoms (p-N1-C1) of the heterocyclic ring (plane 3) is 17.9o whereas that between the corresponding planes of phenyl (plan 2) and the heterocyclic atoms (P-N3-C4) (plane 3) is 26.5o. the reason for the twists from coplanarity of planes 1 and 3 and planes 2 and 4 is the nonbonded repulsion of the ortho hydrogens (on C16 and C22) which are separated by only 2.483 Å. Thus, these of closest approach are a compromise between π orbital overlap as discussed above which would be a maximum with coplanar planes and the non-bonded repulsions.

CONCLUSIONS

Bis(2-phenylaminoethyl)amine hydrochloride **1** was obtained in 25% yield by reacting bis(2-chloroethyl)amine hydrochloride and four molar equivalents of aniline in methanol solvent. From the reaction of bis(2-phenylaminoethyl)amine and $POCl_3$, the bicyclic compound was only obtained in 74% yield. Varying the reaction conditions, e.g., running the reaction in toluene instead of THF, running the reaction at high dilution, or running the reaction at different temperatures did not improve the result. In each case, ^{31}P NMR showed that several products were formed. An explanation for this observation is that $POCl_3$ is very reactive with bases. In bis(2-phenylaminoethyl)amine hydrochloride 7 there are three reactive positions just as there are three reactive chlorines in $POCl_3$. Therefore, in the reaction, there is a possibility of intramolecular mono cyclization, intramolecular by cyclization as well as intramolecular reactions between an attached phosphorus with a bis(2-phenylaminoethyl)amine group.

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