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Synthesis of Aminomethylphosphines with Triazaadamantane Fragments

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Abstract — The reaction of (hydroxymethyl)diphenylphosphine with 7-amino-1,3,5-triazaadamantane, followed by ready oxidation of the initially formed aminomethylphosphine gave diphenyl[(1,3,5-triazaadamantan-7-yl)aminomethyl]phosphine oxide. The reactions of bis(hydroxymethyl)phenylphosphine with 2 mol of 7-amino-1,3,5-triazaadamantane in the absence and in the presence of Paraform provided bis[(1,3,5-triazaadamantan-7-yl)aminomethyl]phenylphosphine and 1,3-bis(1,3,5-triazaadamantan-7-yl)-5-phenyl-1,3,5-diazaphosphorinane, respectively.

Functionalized aminoalkylphosphines are best prepared by nucleophilic substitution reactions of functionalized amines with hydroxyalkyl phosphines. But up to now a few aminomethyl phosphorus derivatives containing functional substituents, most frequently, halogens or carboxy groups [1–4], on the nitrogen atoms have been reported. In this connection we considered it of interest to prepare aminomethylphosphines with substituents of another type, such as 1,3,5-triazaadamantyl, on the nitrogen atom. Triazaadamantane derivatives, by analogy with compounds of the adamantane series (remantadine, amantadine, etc.) may be expected to exibit biological activity [5]. Some cyclic aminomethylphosphines are known to be virus inhibitors [6], and introduction of 1,3,5-triazaadamantyl substituents would considerably affect their biological properies. First representatives of *N*-(1,3,5-triazaadamantan-7-yl)aminomethylphosphine oxides have been prepared by addition of diphenylphosphine to corresponding azomethines [7]. Note that in this case no three-coordinate phosphorus compounds could be obtained.

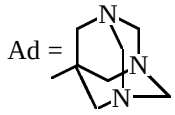
In the present work we reacted bis(hydroxymethyl)-phenylphosphine and (hydroxymethyl)diphenylphosphine with 7-amino-1,3,5-triazaadamantane under various conditions. The reaction of (hydroxymethyl)-diphenylphosphine with 1 mol of 7-amino-1,3,5-triazaadamantane gave a crystalline substance. Its ^{31}P NMR spectrum contained several signals. The strongest were those at –17.73 ppm from the starting (hydroxymethyl)diphenylphosphine and at 26.74 ppm from the product of oxidation of the initially formed aminomethylphosphine, in a 1:2 ratio. From this mixture we could only isolate diphenyl[(1,3,5-triazaadamantan-7-yl)aminomethyl]phosphine oxide (**I**).

$$Ph_2PCH_2OH + H_2N\text{–}Ad \longrightarrow [Ph_2PCH_2NHAd]$$

$$\xrightarrow{[O]} Ph_2P(=O)CH_2NHAd,$$

I

Ad =



Hence, diphenyl[(1,3,5-triazaadamantan-7-yl)-aminomethyl]phosphine, contrary to bis(anilinomethyl)phenylphosphine [8] and bis[(1,3,5-triazaadamantan-7-yl)aminomethyl)]phenylphosphine (**II**) (see below), is susceptible to oxidation. The ^1H NMR spectrum of **I** in benzene-d_6 contains four groups of signals: a singlet of the C–CH_2–N methylene protons at 2.92 ppm, a doublet of the P–CH_2–N methylene protons at 3.16 ppm ($^2J_{HP}$ 9.3 Hz), and two doublets at 3.85 and 4.25 ppm ($^2J_{HH}$ 12.0 Hz) from the AB systems of the triazaadamanyl N–CH_2–N methylene protons. The phenyl protons give a complex multipet at 7.13–7.95 ppm. The integral intensity ratio of these groups of signals is 6:2:6:10, which agrees with the proposed structure of **I**. In the IR spectrum of **I**, there is a broad band at 3288 cm^{-1} due to N–H absorption, and a strong band due to phosphoryl absorption at 1180 cm^{-1}.

The reaction of bis(hydroxymethyl)phosphine with 2 mol of 7-amino-1,3,5-triazaadamantane in benzene resulted in isolation of bis[(1,3,5-triazaadamantan-7-yl)aminomethyl]phenylphosphine (**II**).

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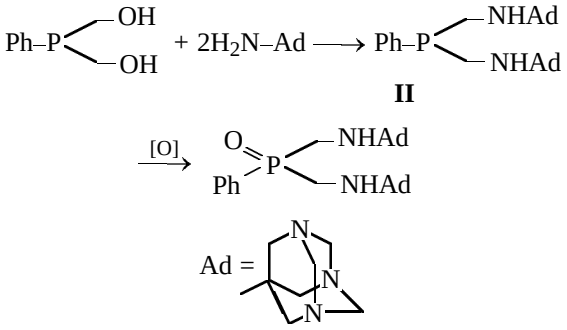
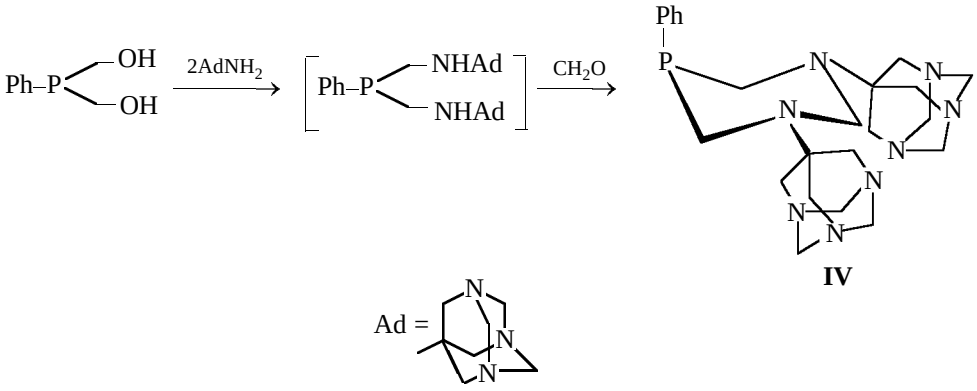


The IR spectrum of compound **II** contains a broad band at 3200–3350 cm due to NH absorption. In the ^{31}P NMR spectrum, a signal at –26.61 ppm is observed. On attempted recrystallization compound **II** oxidized to bis[(1,3,5-triazaadamantan-7-yl)aminomethyl]-phenylphosphine oxide (**III**). We failed to obtain the NMR spectra of **II** and **III** in benzene because of their insufficient solubility, and in DMF the compouds decomposed.

The reaction of bis(hydroxymethyl)phenylphosphine with 2 mol of 7-amino-1,3,5-triazaadamantane in the presence of 1 mol of formaldehyde gave, like in [8], 1,3-bis[(1,3,5-triazaadamantan-7-yl)]-5-phenyl-1,3,5-diazaphosphorinane (**IV**).



The IR spectrum of **IV** lacks OH and NH absorption bands, which points to a cyclic structure. The ^{31}P NMR spectrum of **IV** in benzene contains a single signal at –61.45 ppm, characteristic of 1,3,5-diazaphosphorinanes. The ^{1}H NMR spectrum of **IV** in DMF-d_7 shows that partial decomposition of the product has occurred. The ^{1}H NMR spectrum of this compound in benzene contains five groups of signals: a singlet at 3.34 ppm (C–CH_2–N) and two doublets from the AB systems of the triazadamantanyl N–CH_2–N methylene protons at 4.08 and 4.32 ppm ($^{2}J_{HH}$ 12.0 Hz); the P–CH_2–N protons give a doublet of doublets at 2.84 ppm ($^{2}J_{HH}$ 12.9 Hz and $^{2}J_{PH}$ 6.1 Hz) and a doublet of doublets at 3.29 ppm ($^{2}J_{HH}$ 12.9 Hz, $^{2}J_{PH}$ 5.0 Hz); the doublet of one of the ring N–CH_2–N protons is observed at 3.86 ppm ($^{2}J_{HH}$ 12.1 Hz), and the signal of the second proton overlaps with strong signals of the triazaadamantyl substituents; the phenyl protons are characterized by a multiplet in the range of 7.24–7.59 ppm. The integral intesity ratio points to the presence of two triazaadamantyl fragments in the molecule. The close $^{2}J_{PH}$ constants for axial and equatorial protons of the P–CH_2–N fragment suggest a preferentially axial orientation of the phenyl substituent on phosphorus, though earlier for diazaphosphorinanes with aryl substituents on nitrogen the preferentially equatorial orientation of phenyl on phosphorus and the presence of a conformer with axial orientation of one of the substituents on nitrogen were found [1, 9]. The latter findings were explained by the stabilizing intramolecular orbital interaction in the N–P–C fragment with preferential electron density transfer from the nitrogen lone electrone pair on the P–C bond, which is the largest in the case of axial orientation of the substituent on nitrogen [10]. Evidently, the bulky triazaadamantyl substituents in diazaphosphorinane **IV** prefer equatorial orientation, and the steric structure of the molecule is stabilized by electron density transfer from the phosphorus lone electrone pair on the C–N bond, thus ensuring the preferentially axial orientation of the phenyl group on phosphorus.

Compound **IV**, similarly to known *N*-aryldiazaphosphorinanes, proved rather stable in air. But, if reactions of the latter with alkyl halides yield the corresponding phosphonium salts and do not involve the

nitrogen atoms, the reaction of compound **IV** with methyl iodide gives a complex mixture of unidentified products, probably formed by bond cleavage in the triazaadamantyl fragments and in the diazaphosphorinane ring.

The main difference in the reactivity of 7-amino-1,3,5-triazaadamantane and primary aromatic amines toward bis(hydroxymethyl)phosphine is that in the first case no 1,3,5,7-diazadiphosphacyclooctane is formed even at a 1:1 reactant ratio, while with aromatic amines this type of derivatives is the most stable [1, 8]. The ^{31}P NMR spectra of the reaction mixtures even after prolonged boiling in ethanol, which generally favors conversion of aminomethyl phosphine derivatives of diazadiphosphacyclooctanes [8], contained no signals in the region of –50 ppm, characteristic of the latter compounds. The only cyclic aminomethylphosphine whose signal was observed in the ^{31}P NMR spectrum was diazaphosphorinane **IV**. Besides, signals of various acyclic phosphines and their oxidation products were present.

Inspite of these limitations, the reaction of 7-amino-1,3,5-triazaadamantane with hydroxymethylphosphine proved to be a more universal synthetic approach to *N*-triazaadamantylaminomethylphosphines and their derivatives, than the procedure based on *N*-triazaadamantylazomethines [7], and permitted to prepare several new derivatives of four- and three-coordinate phosphorus.

EXPERIMENTAL

The ^{31}P NMR spectra were recorded on Bruker WM-250 (101 MHz) and Bruker MSL-400 (161 MHz) spectrometers. The ^{1}H NMR spectra were obtained on Bruker WM-250 (250 MHz) and Varian T-60 (60 MHz) spectrometers. The IR spectra of suspensions in Vaseline oil were measured on Specord M-80 and UR-20 spectrometers. All operations with phosphines were carried out an inert atmosphere.

Dipheny[*N*-(1,3,5-triazaadamantan-7-yl)aminomethyl]phosphine oxide (I). Diphenylphosphine, 1.4 g, was added to 0.23 g of formaldehyde, and the reaction mixture was heated on an oil bath until homogenization (120°C). The resulting (hydroxymethyl)diphenylphosphine was dissolved in 10 ml of benzene, 1.16 g of 7-amino-1,3,5-triazaadamantane was added, and the mixture was heated until the latter dissolved. The crystals that formed on cooling (1.85 g) were filtered off and washed with ether. By ^{31}P NMR data, they were a mixture of (hydroxymethyl)diphenylphosphine (δ_P –17.7 ppm) and diphenyl[(1,3,5-triazaadamantan-7-yl)aminomethyl]phosphine oxide (**I**) (δ_P 26.74 ppm) in a 1:2 ratio. Crystallization of 1 g of this mixture gave 0.37 g (13%) of pure compound **I**, mp 213–214°C. IR spectrum, ν, cm^{-1}: 3288 (N–H), 1180 (P=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.92 s (6H, C–CH$_2$–N), 3.16 d (2H, P–CH$_2$–N, $^{2}J_{PH}$ 9.3), 3.85 d (3H, N–CH^{a}–N, $^{2}J_{HH}$ 12.0), 4.25 d (3H, N–CH^{b}–N, $^{2}J_{HH}$ 12.0), 7.03–7.95 m (10H, C$_6$H$_5$–P). ^{31}P NMR spectrum (C$_6$D$_6$): δ_P 26.74 ppm. Found, %: C 64.86, H 7.01, N 15.41, P 8.08. $C_{20}H_{25}N_4OP$. Calculated, %: C 65.22, H 6.79, N 15.22, P 8.42.

Bis[(1,3,5-triazaadamantan-7-yl)aminomethyl]phenylphosphine (II). To a solution of 0.4 g of bis(hydroxymethyl)phenylphosphine in 15 ml of benzene, 0.72 g of 7-amino-1,3,5-triazaadamantane was added, and the mixture was heated until the amine dissolved. After cooling to room temperature, crystals of **II** formed and were filtered off and washed with benzene and acetone. An analytical sample was crystallized from 1:1 benzene–DMF. Yield 0.5 g (48%), mp 207°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 3280 (N–H). ^{31}P NMR spectrum (DMF): δ_P –26.61 ppm. Found, %: C 60.08, H 8.21, N 25.08, P 6.73. $C_{22}H_{35}N_8P$. Calculated, %: C 59.72, H 7.92, N 25.34, P 7.01.

When crystallized in air, compound **II** oxidized to give **bis[(1,3,5-triazaadamantan-7-yl)aminomethyl]phenylphosphine oxide (III).** mp 242°C. ^{31}P NMR spectrum (DMF): δ_P 34.11 ppm. Found, %: C 56.92, H 7.70, N 23.96, P 6.71. $C_{22}H_{35}N_8OP$. Calculated, %: C 57.64, H 7.64, N 24.45, P 6.77.

1,3-Bis(1,3,5-triazaadamantan-7-yl)-5-phenyl-1,3,5-diazaphosphorinane (IV). Paraform, 0.57 g, was added to 0.7 g of phenylphosphine, and the mixture was heated to on a water bath until homogenization. The resulting bis(hydroxymethyl)phenylphosphine was mixed with 10 ml of benzene and 1.95 g of 7-amino-1,3,5-triazaadamantane was added. The reaction mixture was stirred for 15 min at room temperature and then heated to the boil. A viscous substance precipitated on walls of the flask. Its major component was product **IV**. After cooling to room temperature, the benzene solution was decanted and evaporated to leave crystals of compound **IV**, which were filtered off and washed with benzene. The viscous substance remaining on walls of the flask was crystallized from benzene to give pure **IV**. Both portions of compound **IV** were combined. Yield 1.15 g (40%), mp 198°C. ^{1}H NMR spectrum (C$_6$D$_6$), δ, ppm (*J*, Hz): 2.84 d.d (2H, P–CH^{a}–N), 3.29 d.d (2H, P–CH^{e}–N, $^{2}J_{HH}$ 12.0, $^{2}J_{PH}$ 5.0), 3.34 s (12H, C–CH$_2$–N), 3.86 d (1H, N–CH^{2}–N$_{ring}$, $^{2}J_{HH}$ 12.1), 4.08 d (7H, N–CH^{a}–N$_{ad}$ + N–CH^{e}–N$_{ring}$, $^{2}J_{HH}$ 12.0), 4.32 d (6H, N–CH^{b}–N$_{ad}$, $^{2}J_{HH}$ 12.0), 7.24–7.59 m (5H, C$_6$H$_5$–P).

^{31}P NMR spectrum (C_6H_6): δ_P –61.45 ppm. Found, %: C 60.23, H 8.09, N 24.04, P 7.17. $C_{23}H_{35}N_8P$. Calculated, %: C 60.79, H 7.71, N 24.67, P 6.83.

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