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ALKYLATION OF AMINOMETHYL DERIVATIVES OF PRIMARY PHOSPHINES

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The alkylation of aminomethyl derivatives of secondary phosphines has been studied [1]. It was shown that the course of alkylation depends on the alkylating agent used and the bulk of the substituents on the P and N atoms. In the absence of steric hindrance, addition occurs at the P atom. Use of an excess of alkylating agent results in alkylation of both heteroatoms. Occasionally, transaminomethylation of the starting aminomethyl derivatives of secondary phosphines at the P atom occurs. In the case of 1,3,5-triaza-7-phosphaadamantane alkylation takes place at the N atom [2]. The alkylation of aminomethyl derivatives of primary phosphines (AMP) has not been described [3].

We here consider the alkylation of di(aminomethyl)phenylphosphines, 1,3,5-diazophosphorinanes, and 1,5-diaza-3,7-diphosphacyclooctanes with alkyl halides.

Treatment of di(phenylaminomethyl)phenylphosphine (I) with an excess of methyl iodide results in methylation at phosphorus only, to give the phosphonium salt (II)

$$\underset{(I)}{PhP(CH_2NHPh)_2} + MeI \rightarrow \underset{(II)}{Ph(Me)\overset{+}{P}(CH_2NHPh)_2I^-}$$

The course of the alkylation was established by the chemical shift in the ^{31}P NMR spectrum from −31 ro +22 ppm, and the conservation in the IR spectra of the band at 3400 cm^{-1}, characteristic of secondary amines. Treatment of bis(diethylaminomethyl)phenylphosphine with an excess of MeI results in addition to both P and N to form the phosphonioammonium salt (IV)

$$\underset{(III)}{PhP(CH_2NEt_2)_2} + MeI \rightarrow Ph(Me)\overset{+}{P}\begin{matrix}CH_2\overset{+}{N}(Me)Et \\ \\ \underset{(IV)}{CH_2NEt_2}\end{matrix} \quad 2I^-$$

The ^{31}P NMR spectrum shows a shift in the signal from −50 to +20 ppm. The elemental analysis of the product corresponded to the addition of two molecules of MeI. Double methylation products of (I), monomethylation of (III), and triple methylation of (I)-(III) were not found in the reaction mixtures (^{31}P NMR).

$$\underset{(V)}{PhP(O)(CH_2NHC_6H_4Me\text{-}p)_2} + MeI \rightarrow Ph-\overset{O}{\overset{\|}{P}}\begin{matrix}CH_2NHC_6H_4Me\text{-}p \\ \\ \underset{\underset{(VI)}{Me}}{CH_2\overset{+}{N}HC_6H_4Me\text{-}p}}\end{matrix} \quad I^-$$

The studies made in [1] concerned only the methylation of aminomethyl derivatives with aliphatic substituents on the nitrogen atom. With an excess of MeI, in every instance double methylation products were obtained. The methylation of di-(p-tolylaminomethyl)phenylphosphine oxide (V) resulted in methylation at one of the nitrogen atoms to give (VI). The IR spectrum of (VI) showed bands at 3280 and 2600 cm^{-1}, characteristic of secondary and quaternary amines. The elemental analysis confirmed the addition of one molecule of MeI.

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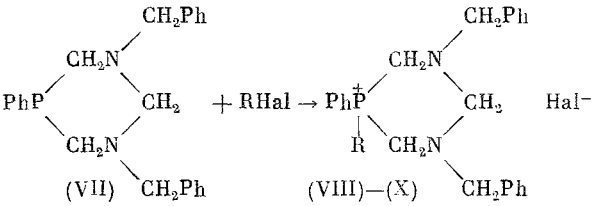
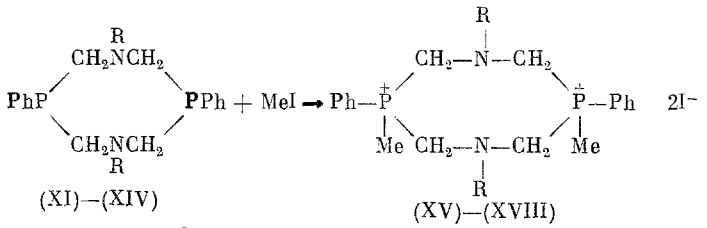
The alkylation of cyclic AMP was studied using 1,3,5-diazaphosphorinanes and 1,5-diaza-3,7-diphosphacyclooctanes as examples. 1,3-Dibenzyl-5-phenyl-1,3,5-diazaphosphorinane (VII) was treated with an excess of EtI, PrI, and octadecyl bromide at 25-40°C. In all cases, only one molecule of the alkyl halide added to the P atom. This was confirmed by elemental analyses and the change in δ ^{31}P from −61 to −2 ppm



(VII) (VIII)—(X)

R = Et, Hal = I (VIII); R = Pr, Hal = I (IX); R = $C_{18}H_{37}$, Hal = Br (X).

Methylation of N,N-disubstituted-1,5-diaza-3,7-diphosphacyclooctanes(XI)-(XIV) was effected under the same conditions. From elemental analyses, two molecules of MeI were added at the P atoms



(XI)—(XIV) (XV)—(XVIII)

R = Ph (XI), (XV); *p*-MeC_6H_4 (XII), (XVI); *p*-BrC_6H_4 (XIII), (XVII); $PhCH_2$ (XIV), (XVIII).

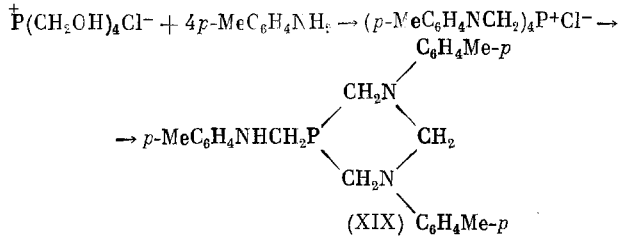
This was confirmed by the splitting of the methyl signal into two components in the PMR spectrum. The ^{31}P NMR spectra of the methiodides showed signals at 23-13 ppm typical of phosphonium salts. The proton-decoupled spectrum of the solution in CF_3COOH showed no changes. The constancy of the signal, and the identity of the chemical shifts of the signals of the compounds in CF_3COOH, which protonates the heteroatom, and in DMF, provides further confirmation of methylation at the P atom.

A comparison of the alkylation of cyclic AMP with 6- and 8-membered rings showed that they proceed similarly.

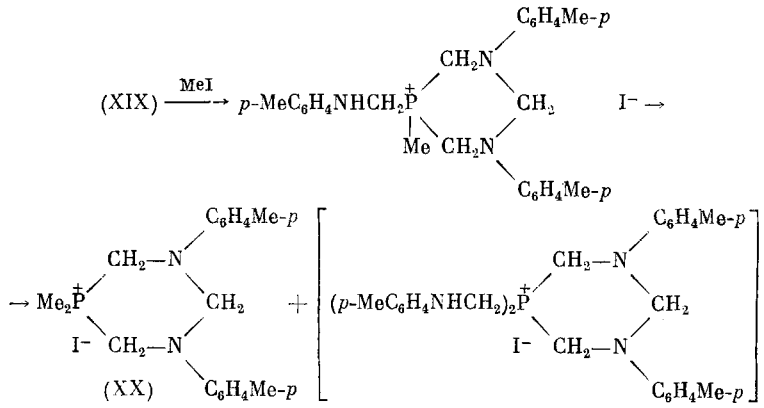
A study has been made [2] of the addition of methyl iodide to 1,3,5-triaza-7-phosphaadamantane, which occurs at one of the N atoms. This example, together with the findings described above for the alkylation of di(aminomethyl)phenylphosphines, 1,3,5-diazaphosphorinane, and 1,5-diaza-3,7-diphosphacyclooctanes confirms the great sensitivity of systems containing the P-C-N fragment to steric effects. The most likely reason for alkylation at nitrogen in 1,3,5-triaza-7-phosphaadamantane is the almost pure S-character of the unshared electron pair (UEP) of the P atom, which results in its having low reactivity in reactions with electrophilic reagents. From x-ray structural studies [4], the angles at the P atom in this compound are 96°, whereas the angles at the N atom have values corresponding to the sp^3-hybridized state. In noncyclic aminomethylphosphines, the angles at the P atom increase as a result of the steric influence of the substituents, resulting in a decrease in the S-character of the UEP of the P atom and an increase in its reactivity toward electrophilic reagents. The sums of the angles at the P atom in 1,3,5-diazaphosphorinanes [5] and 1,5-diaza-3,7-diphosphacyclooctanes [6] are in aggregate greater than the sums of the angles at the P atom in 1,3,5-triaza-7-phosphaadamantane by approximately 12°, mainly by virtue of the extracyclic angles.

The results of x-ray structural examinations of (VII) and (XIV) show that the substituents on the nitrogen atoms are axially oriented. This could be due to the transfer of electron density from the UEP of the N atom to the vacant orbital of the P—C bond, which is at a maximum when the P—C bond and the UEP are in the trans positions [5, 7]. Transfer of electron density results in a reduction in the reactivity of the UEP, which provides an explanation for the absence of alkylation at nitrogen in these cyclic AMP. Alkylation of the P atoms hinders the addition of a second molecule of the alkylating agent at nitrogen.

Tetrakis(hydroxymethyl)phosphonium chloride reacts with p-toluidine to give 1,3-di-p-tolyl-5-p-tolylaminomethyl-1,3,5-diazaphosphorinane (XIX). This reaction apparently proceeds via the intermediate tetrakis(p-tolylaminomethyl)phosphonium chloride, which disproportionates in the presence of triethylamine in the same way as tetrakis(anilinomethyl)phosphonium chloride [8]

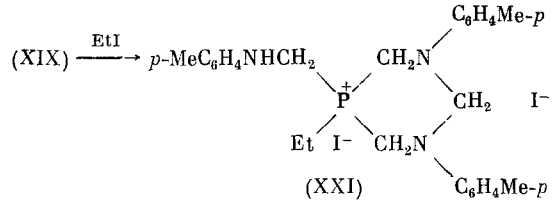


The reaction of (XIX) with MeI is of interest. The spectrum of the reaction mixture lacks the signal for (XIX) at −48 ppm, and in its place a new signal appears at 3 ppm which was found to be due to 1,3-di-p-tolyl-5,5-dimethyl-1,3,5-diazaphosphorinane iodide (XX). The IR spectrum of (XX) showed no absorption for secondary amines, and the low chemical shift in the ^{31}P NMR spectrum indicates that the P atom is tetracoordinated. The elemental analysis confirmed this structure. The formation of (XX) may be represented as follows



According to this scheme, symmetrization of the initially formed methylation product occurs. The formation has been observed [1] of a "transaminomethylation" product in the reaction of MeI with morpholinomethyldiisopropylphosphine, namely di(morpholinomethyl)diisopropylphosphonium iodide. This reaction and that described above jointly give both symmetrization products.

The initially formed alkylation product can be isolated when (XIX) reacts with EtI:



The IR spectrum of (XXI) shows absorption at 3200 cm^{-1} corresponding to a secondary amine, the value of the ^{31}P chemical shift (9.1 ppm) indicates alkylation at phosphorus, and the elemental analysis confirms the addition of a single molecule of EtI.

EXPERIMENTAL

IR spectra were obtained on a UR-10 spectrometer in oil, and ^{31}P NMR spectra on a KGU-4 NMR spectrometer (10.2 MHz) with noise decoupling from protons (25.2 MHz), from 85% H_3PO_4 (positive values at low field).

Di(phenylaminomethyl)phenylmethylphosphonium Iodide (II). To 1.2 g (3.8 mmole) of (I) [9] in 6 ml of acetone was added 1 ml of MeI. After 1 h, the mixture was evaporated, and the

residue crystallized from acetone to give 1.1 g (63%) of (II), mp 154°C, δ ^{31}P 22 ppm (DMF). IR spectrum (ν, cm^{-1}): 3200 (NH, oil). Found: C 54.80; H 5.52; P 7.01; N 5.80%. $C_{21}H_{24}PN_2I$. Calculated: C 54.55; H 5.19; P 6.71; N 6.06%.

Phosphonioammonium Salt (IV). To 2.8 g (10 mmole) of (II) [10] in 30 ml of acetone at 10°C was added 4 ml of MeI. After 1 h the mixture was kept under vacuum (1 mm) for 1 h at 80°C. The residue was a viscous, undistillable liquid which darkened in light, yield 100%. δ ^{31}P 20 ppm. Found: C 38.01; H 6.42; P 5.37%. $C_{18}H_{35}PN_2I_2$. Calculated: C 39.30; H 6.21; P 5.50%.

Di(p-tolylaminomethyl)phenylphosphine Oxide (V). To 17 g (0.1 mole) of di(hydroxymethyl)phenylphosphine was added 21.4 g (0.2 mole) of p-toluidine. Heat was evolved, and water separated (δ ^{31}P of the reaction mixture, −31 ppm). After 5 h, 15 ml of 28% H_2O_2 in 50 ml of acetone was added. On the following day, the solid was filtered off and crystallized from acetone. Yield of (V), 29 g (80%), mp 168°C, δ ^{31}P 33 ppm (DMF). Found: C 72.44; H 7.16; P 8.62; N 7.41%. $C_{22}H_{25}PN_2O$. Calculated: C 72.53; H 6.87; P 8.54; N 7.69%.

Ammonium Salt (VI). Compound (V) (0.8 g, 2.1 mmole) was dissolved in 1 ml of MeI at 40°C. After 2 h, 2 ml of MeOH was added, and the solid isolated and crystallized from MeOH. Yield of (VI), 0.6 g (55%), mp 127°C, δ ^{31}P 36 ppm (DMF). IR spectrum (ν, cm^{-1}): 3250 (NH), 2600 ($\overset{+}{N}$H, oil). Found: C 54.26; H 5.80; P 5.88; N 5.79%. $C_{23}H_{28}PN_2OI$. Calculated: C 54.55; H 5.53; P 6.13; N 5.53%.

1,3-Dibenzyl-5-ethyl-5-phenyl-1,3,5-diazaphosphoniarinane Iodide (VIII). 1.8 g (5 mmole) of (VII) [9] was dissolved in 3 ml of EtI. The solution was kept uncovered. On the following day, the residue was recrystallized from MeOH to give (VIII), 2.2 g (85%), mp 175-177°C, δ ^{31}P 3 ppm (DMSO). Found: C 58.04; H 5.84; P 5.65; N 5.37%. $C_{25}H_{30}PN_2I$. Calculated: C 58.14; H 5.81; P 6.01; N 5.43%.

1,3-Dibenzyl-5-propyl-5-phenyl-1,3,5-diazaphosphoniarinane Iodide (IX). To 1.5 g (5 mmole) of (VII) was added 3 ml of PrI. The mixture was kept for 10 h at 40°C, and the residue crystallized from MeOH to give (IX), 1.9 g (86%), mp 181-184°C, δ ^{31}P 0 ppm (DMF). Found: C 58.88; H 6.05; P 5.64%. $C_{26}H_{32}PN_2I$. Calculated: C 58.87; H 6.04; P 5.85%.

1,3-Dibenzyl-5-phenyl-5-octadecyl-1,3,5-diazaphoniarinane Bromide (X). To 1.1 g (3 mmole) of (VII) was added 1 g (3 mmole) of octadecyl bromide in 7 ml of MeOH. The mixture was kept for 15 h at 50°C. On cooling the mixture, a solid separated which was filtered off and crystallized from MeCN. Yield of (X), 1.8 g (85%), mp 115°C, δ ^{31}P 0 ppm (DMSO). Found: C 70.98; H 8.90; P 4.59%. $C_{41}H_{62}PN_2Br$. Calculated: C 71.00; H 8.95; P 4.47%.

1,3,5,7-Tetraphenyl-3,7-dimethyl-1,5-diaza-3,7-diphosphoniacyclooctane Diiodide (XV). To 2 g (9 mmole) of (XI) [11] was added 1 ml of MeI in 8 ml of MeCN. On the following day, the solid was filtered off and recrystallized from MeCN to give (XV), 2.9 g 90%), mp 210°C, δ ^{31}P 22 ppm (DMF). Found: C 48.73; H 4.72; P 7.75; N 4.17%. $C_{30}H_{34}P_2N_2I_2$. Calculated: C 48.78; H 4.61; P 8.40; N 3.79%.

(XVI)-(XVIII) were obtained similarly from (XII)-(XIV) [11], respectively. Given below are yield, mp, δ ^{31}P, found, molecular formula, calculated.

(XVI). 38%, 178°C, 23 ppm (DMF). C 49.57; H 5.31; P 7.90; N 3.71%. $C_{32}H_{38}P_2N_2I_2$. C 50.13; H 4.96; P 8.09; N 3.66%.

(XVII). 35%, 190°C, 16 ppm (DMF). C 40.23; H 3.48; P 6.60; N 3.96%. $C_{30}H_{33}P_2N_2Br_2I_2$. C 40.17; H 4.57; P 6.92; N 3.13%.

(XVIII). 95%, 172°C, 14 ppm (DMF). C 50.24; H 4.93; P 7.56; N 3.82%. $C_{32}H_{38}P_2N_2I_2$. C 50.13; H 4.96; P 7.56; N 3.66%.

1,3-Di-p-tolylaminomethyl-1,3,5-diazaphosphorinane (XIX). To 7.7 h (0.04 mole) of tetrahydroxymethylphosphonium dichloride in 120 ml of EtOH was added 17.3 g (0.16 mole) of p-toluidine. The toluidine dissolved, and a solid separated. After 2 h, the solid was filtered off and dissolved in 300 ml of acetone mixed with 50 ml of Et_3N. After 1.5 h, a precipitate of $Et_3N \cdot HCl$ separated, yield 3.5 g (63%). The filtrate was evaporated, and the residue crystallized from EtOH to give (XIX), 10.8 g (66%), mp 131°C, δ ^{31}P 48 ppm (DMF, pyridine). IR spectrum (ν, cm^{-1}): 3240 (NH, oil). Found: C 74.13; H 7.27; P 8.08; N 10.05%. $C_{25}H_{30} \cdot \cdot PN_3$. Calculated: C 74.44; H 7.44; P 7.69; N 10.42%.

1,3-Di-p-tolyl-5,5-dimethyl-1,3,5-diazaphosphoniarinane Iodide (XX). 1.48 g (3.7 mmole) of (XIX) was dissolved in 5 ml of MeI. On the following day, 10 ml of EtOH and 0.1 g (4 mmole) of Na were added. Following the formation of a homogeneous solution, the solvent was removed. The residue (a gummy liquid) on trituration with ether gave a fine, bright yellow powder. It was dissolved in EtOH, and allowed to crystallize over several weeks at about 20°C. The crystals were isolated and recrystallized from MeCN. Yield of (XX) 15%, mp 216-217°C, δ ^{31}P 3 ppm (DMF). The IR spectrum showed no absorption for NH. Found: C 52.01; H 6.01; P 7.03; N 6.15%. $C_{19}H_{26}PN_2I$. Calculated: C 51.82; H 5.91; P 7.05; N 6.36%.

1,3-Di-p-tolyl-5-ethyl-5-p-tolylaminomethyl-1,3,5-diazaphosphoniarinane Iodide (XXI). To 0.6 g (1.5 mmole) of (XIX) was added 2 ml of EtI, the mixture kept at 40°C for 15 h, and the excess of EtI removed. The residue on trituration with ether gave a yellow powder. Yield of (XXI) 0.73 g (88%), mp 80°C (decomp.), δ ^{31}P 9 ppm (pyridine). IR spectrum (ν, cm^{-1}): 3200 (NH, oil). Found: C 57.71; H 6.19; P 5.12; N 7.12%. $C_{27}H_{35}PN_2I$. Calculated: C 57.96; H 6.26; P 5.55; N 7.51%.

CONCLUSIONS

1. Di(phenylaminomethyl)phenylphosphine, N,N-disubstituted-5-phenyl-1,3,5-diazaphosphorinanes, and 1,5-diaza-3,7-diphosphacyclooctane, on treatment with excess alkyl halide, are alkylated only at the P atom. In the case of bis(diethylaminomethyl)phenylphosphine, addition occurs at both phosphorus and nitrogen.

2. Reaction of 1,3-di-p-tolyl-5-tolylaminomethyl-1,3,5-diazaphosphorinane with alkyl halides affords P alkylation products with one and two moles of alkylating agent.

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