Chemical Proof for the Preferred Nitrogen Quarternization in 1,3,5-Triaza-7-phosphaadamantane

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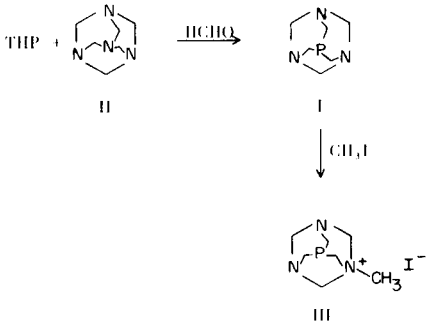
Isolation of 1,3,5-triaza-7-phosphaadamantane (I) in 40% yield from the reaction mixture of tris(hydroxymethyl)phosphine (THP), hexamethylenetetramine (II), and formaldehyde was reported recently (2). 1-Methyl-1-



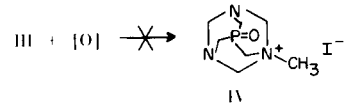
azonia-3,5-diaza-7-phosphaadamantane iodide (III) was prepared and shown by nuclear magnetic resonance spectra to be an ammonium salt rather than a phosphonium derivative.

The authors have since increased the yield of I and have shown by chemical reactions that III is an ammonium salt.

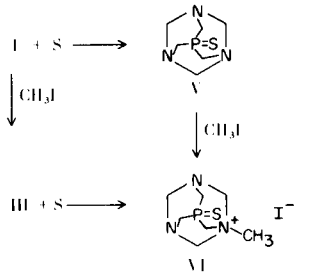
Addition of a large excess of formaldehyde (0.5 mole, instead of 0.1 mole per 0.025 mole of THP) increased the yield of I. The use of sodium hydroxide-neutralized tetrakis(hydroxymethyl)phosphonium chloride (Thpc) as the source of THP produced yields averaging 71.9%.

Quaternization of tertiary phosphine in competition with a tertiary amine group has often been reported in the literature. Ordinarily, phosphines because of their high nucleophilicity, readily exchange with quaternary ammonium salts to form phosphonium salts (3). Mann (4), working with hexahydro-1,4-diphenyl-1,4-azaphosphine, showed by infrared spectra that when monoquaternization occurs, the tertiary phosphine, rather than the amine, undergoes reaction. Nuclear magnetic resonance spectra have been used with dimethylphosphinomethyldimethylamine (5) to determine the site of alkylation. The authors, however, concluded only that the reaction with methyl iodide produced a mixture of *P*- and *N*-monomethylated products and they did not report any data or isolate compounds from such a reaction.

To provide a chemical method for resolving structures of compounds when nitrogen was quaternized preferentially to phosphorus, attempts were made to convert the trivalent phosphorus to pentavalent. This method must not affect the amine or ammonium group. By oxidation, we hoped to convert III into 1-methyl-1-azonia-3,5-diaza-7-phosphaadamantane 7-oxide iodide (IV), a compound prepared earlier (2).



Use of 3% hydrogen peroxide or tertiary butylhydroperoxide at room temperature produced only a brown intractable residue. Since IV is a known, stable compound, evidence cited above suggests that III is peroxide sensitive. Sulfur reacted with I to produce 1,3,5-triaza-7-phosphaadamantane 7-sulfide (V) in excellent yield. The methyl iodide derivative, 1-methyl-1-azonia-3,5-diaza-7-phosphaadamantane 7-sulfide iodide (VI) was prepared from the reaction of methyl iodide and V in benzene. This same product, VI, was prepared by the reaction of III with sulfur in benzene.



The reaction of tertiary phosphine sulfides with alkyl halides to form onium salts (6,7) was suspected in the conversion of V to VI. However, recrystallization of this compound from water or a water-methanol solution did not produce the obnoxious smelling methyl mercaptan and phosphaadamantane 7-oxide. The best solvent pair for recrystallization, was DMSO-acetone since unreacted phosphaadamantane 7-sulfide was not soluble in DMSO and

was easily filtered from the methyl iodide salt.

The P^{31} nuclear magnetic resonance spectra furnished further proof that III is an ammonium salt since a spectrum of I showed a 7 line multiplet centered at +100 ppm (reference phosphoric acid) and the P^{31} nmr spectrum of III showed a multiplet centered at +87 ppm. If III were a phosphonium salt, the P^{31} nmr spectrum should have shown a multiplet centered between 0 and -100 ppm (8).

The phosphaadamantane 7-sulfide V and its derivative, VI are not as soluble in water and chloroform as I and III. All three phosphaadamantanes sublime: I at 130° at 0.05 mm, III and V at 160° at 0.05 mm.

EXPERIMENTAL

Preparation of I from Tetrakis(hydroxymethyl)phosphonium Chloride (Thpc) (9).

To a solution of Thpc (23 g., 75.8%, 0.947 mole), neutralized (*p*H = 7) by sodium hydroxide (63.85 g., 50%, 0.798 mole), was added formalin (400 g., 37%, 5 moles). Hexamethylenetetramine (140 g., 1 mole) was added to the solution and the solution kept at room temperature overnight (17 hours). Evaporation of about 80% of the water at room temperature, filtration, and a cold ethanol wash (200 ml.) produced 106.9 g. (71.9% yield based on Thpc) of I.

Preparation of 1,3,5-Triaza-7-phosphaadamantane 7-Sulfide (V).

Sulfur (flowers of sulfur, 1.5 g., 0.047 mole) and I (6.28 g., 0.04 mole) were refluxed in 125 ml. of ethanol-125 ml. of benzene solution for 2 hours. The solution was filtered and yielded 7.5 g. (94.6% yield) of V. The analytical sample was recrystallized from water. The infrared spectrum of a potassium bromide pellet of V showed bands at 3.4 (W), 3.45 (W), 6.95 (M), 7.1 (M), 7.35 (W), 7.85 (S), 8.13 (M), 9.14 (M), 9.72 (W), 9.97 (S), 10.31 (S), 10.6 (S), 11.12 (M), 12.4 (M), 12.5 (M), 12.9 (M), 13.5 (S), and 13.75 μ (S).

Anal. Calcd. for $C_6H_{12}N_3PS$: C, 38.08; H, 6.39; N, 22.06; P, 16.37; S, 16.95. Found: C, 38.04; H, 6.45; N, 22.29; P, 16.22; S, 17.02.

Preparation of 1-Methyl-1-azonia-3,5-diaza-7-phosphaadamantane 7-Sulfide (VI) from V.

Methyl iodide (0.5 g., 0.0035 mole) and V (0.65 g., 0.0034 mole) were refluxed in 40 ml. of benzene from 1.5 hours. The solution was filtered to yield 1.0 g. (88.5% yield) of crude VI, m.p. 208-209° (DMSO-acetone). The infrared spectrum of a potassium bromide pellet of VI showed bands at 3.31 (W), 3.38 (W), 6.91 (M), 7.14 (M), 7.67 (M), 7.83 (W), 8.02 (W), 8.4 (W), 8.8 (W), 9.0 (M), 9.2 (M), 9.78 (M), 9.9 (M), 10.18 (M), 10.88 (M), 11.15 (M), 11.5 (W), 12.52 (M), 13.4 (S), and 14.45 μ (M).

Anal. Calcd. for $C_7H_{15}N_3PSI$: C, 25.28; H, 4.53; N, 12.69; P, 9.37; S, 9.67; I, 38.37. Found: C, 25.58; H, 4.71; N, 12.54; P, 9.29; S, 9.66; I, 38.51.

Preparation of VI from III.

Sulfur (0.1 g., 0.003 mole) and III (0.85 g., 0.0028 mole) were refluxed in 40 ml. of benzene for 4 hours. The solution was filtered to yield 0.75 g. (80% yield) of crude VI. This material was recrystallized from DMSO-acetone and found to be VI by mixture melting point determination and infrared spectra comparison with authentic material.

Acknowledgment.

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