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The Reaction of *o*-Phenylenediamine with Phenyl Phosphorodichloridate[1]. Synthesis and Reactions of 2-Phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole-2-oxide and Related Compounds

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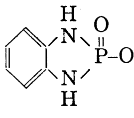
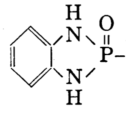
The reaction of *o*-phenylenediamine with phenylphosphorodichloridate was reexamined. Unlike Autenrieth and Bolli's report, 2-phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole 2-oxide (I) has not been obtained by their procedure. Instead, phenyl hydrogen N-(2-aminophenyl)phosphoroamidate (V) was obtained by the reaction in refluxing benzene. When the reaction was carried out by the fusion method, a roughly equal amount of V and *o*-phenylenediamine salt of diphenyl phosphate (VI) were isolated. The solubility and reactivity of both compounds V and VI were compared with those of the Autenrieth and Bolli's compound and it was concluded that their synthesis should be refuted. Finally the diazaphosphole I was synthesized by the reaction in bromobenzene and the properties of I was quite different from those of the Auterieth and Bolli's compound.

In 1925, Autenrieth and Bolli reported[3] the synthesis of 2-phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole 2-oxide (I) by the reaction of o-phenylenediamine with phenyl phosphorodichloridate in refluxing benzene or by fusion of both compounds without solvent above 170°. The compound they obtained was reported to be insoluble in common organic solvents and stable to acid. Later, compounds II[4] and III[5] with the same diazaphosphole ring have been synthesized by the reaction of phenylphosphonic dichloride or phenylphosphonic diamide with the corresponding *o*-diamines. Compounds II and III were shown to be hydrolyzed in both acidic and alkaline conditions. II was found to be hydrolyzed even in hot water to give the ring opened compound IV.


I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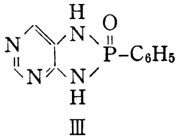
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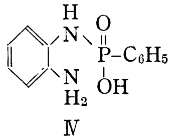
IV

The reported stability of the Autenrieth and Bolli's compound (I) to acid is quite contrasting from the reactivity of II and III. Considering the general instability of five membered cyclic phosphorus compounds due to the ring strain and the relief of the strain by the formation of pentacovalent phosphorus intermediate,[6] the facile hydrolysis of II and III is quite reasonable. The easy hydrolysis of ordinary phosphoramidates under acidic condition also supports the instability of II and III to acid. On the basis of these considerations, the stability of the Autenrieth and Bolli's compound is rather queer and has been questioned. In their paper,

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1) A part of this study was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.

2) Location: *Gofuku, Toyama.*

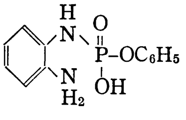
3) W. Autenrieth and E. Bolli, *Chem. Ber.*, **58**, 2144 (1925).

4) *a*) R.L. Dannley and P.L. Wagner, *J. Org. Chem.*, **26**, 3995 (1961); *b*) V. Gutman, D.E. Hagen, and K. Utvary, *Monatsh.*, **93**, 627 (1962).

5) J.H. Lister and G.M. Timmis, *J. Chem. Soc.* (*C*), **1966**, 1242.

6) F.H. Westheimer, *Accounts of Chemical Research*, **1**, 70 (1968).

Dannley, and Wagner have noted on the difference and described that the stability of the Autenrieth and Bolli's compound might have been due to the insolubility in dilute aqueous acid. Recently Edmundson7) examined the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate and obtained a single product of mp 175—176°, whose structure was determined as phenyl hydrogen N-(2-aminophenyl)-phosphoroamidate (V) by comparing the infrared (IR) spectrum with those of IV and related compounds. He also mentioned that the attempted synthesis of the benzodiazaphosphole I under various conditions was unsuccessful and suggested that the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate does not yield the diazaphosphole I, and the Autenrieth and Bolli's paper should be refuted. However, Edmundson has not examined another Autenrieth and Bolli's reaction condition, *vz.* fusion of *o*-phenylenediamine with phenyl phosphorodichloridate.


V

It is then considered necessary to reexamine carefully the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate under various conditions including Autenrieth and Bolli's conditions and to check if the diazaphosphole I is really formed as has been reported.

This paper deals with the results along this line and also reports the first correct synthesis of the diazaphosphole (I).

When *o*-phenylenediamine was treated with half a molar equivalent of phenyl phosphorodichloridate in refluxing benzene for four hours and worked up according to the Autenrieth and Bolli's procedure, a crystalline compound of mp 175—177° was obtained in 44% yield. The infrared spectrum showed that the compound was identical with Edmundson's compound V. The compound is insoluble in benzene, chloroform, ether, and ethyl acetate. It is soluble in hot water and hot ethanol. Although the solubility of V is consistent with that of the Autenrieth and Bolli's compound (I), the reaction of V was quite different from that reported by them.3)

When V was heated with dilute hydrochloric acid, phenyl phosphate and *o*-phenylenediamine dihydrochloride were obtained in good yields. V reacts with water by sixteen hours' reflux to give *o*-phenylenediamine salt of phosphoric acid and phenol. It is of interest that V reacts with methanol by twentyfour hours' reflux to give *o*-phenylenediamine salt of methyl phenyl phosphate in a good yield. The application of this reaction to various alcohols is now in progress (Chart 1).

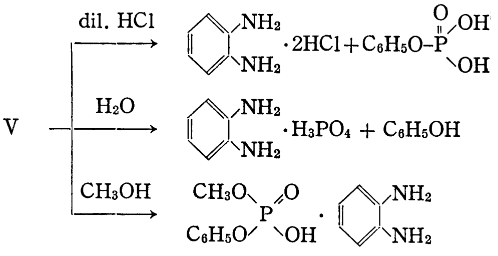


Chart 1

Since the reported synthesis of the benzodiazaphosphole I in refluxing benzene gave phenyl hydrogen N-(2-aminophenyl)phosphoroamidate V, another reported reaction condition, fusion of *o*-phenylenediamine with phenyl phosphorodichloridate, has also been repeated. *o*-Phenylenediamine was mixed with half a molar equivalent of phenyl phosphorodichloridate and heated around 170—180° for 2.5 hours without solvent. Work-up as reported gave a new crystalline compound (VI) of mp 183—184° in a yield of 25% along with an equal amount of V. The elemental analysis of VI showed that the compound has a molecular formula of $C_{18}H_{19}O_4N_2P$. The molecular formula and IR spectrum suggested VI as *o*-phenylenediamine salt of diphenyl phosphate and it was identified by the comparison of IR and melting point with a standard specimen.

As phenyl phosphorodichloridate was analytically pure as described in the experimental section, the formation of VI should be explained by the disproportionation of a monophenyl

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7) R.S. Edmundson, *J. Chem. Soc.* (*C*), **1969**, 2730.

compound to a diphenyl compound during the reaction. The details of the mechanism of the disproportionation reaction is now being investigated. In this respect it is of interest that Edmundson has recently reported the synthesis of phenyl hydrogen N-(2-aminophenyl) phosphoroamidate by the reaction of *o*-phenylenediamine with diphenyl phosphite in carbon tetrachloride.[8]

As expected, VI was recovered unchanged when it was refluxed with water, methanol, and aqueous ammonium chloride. The compound was also stable to dilute acetic acid after 7 hours' reflux. However, when it was refluxed in dilute hydrochloric acid for 16 hours, *o*-phenylenediamine dihydrochloride, diphenyl phosphate and phenyl phosphate were obtained in fair yields. The observation was inconsistent with the reaction of the Autenrieth and Bolli's compound (I).

As described above, I was not obtained by the Autenrieth and Bolli's conditions and the product V and VI obtained instead showed different properties from those reported. We, therefore, have undertaken the synthesis of I under various conditions and finally succeeded in isolation and characterization of I by carrying out the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate in bromobenzene. A 1:1 mixture of *o*-phenylenediamine and phenyl phosphorodichloridate was refluxed in bromobenzene and the reaction was traced by the titration of the evolved hydrogen chloride. After the evolution of the theoretical amount of hydrogen chloride, the reaction mixture was kept at room temperature. Considerable amounts of the unidentified solid material of mp 243—248° was filtered off and the clear solution was kept in a refrigerator to give colorless needles of mp 151—153° in 17% yield. Mass spectrum (M^+ 246) and elemental analysis showed that the compound has a molecular formula of $C_{12}H_{11}O_2N_2P$. IR spectrum of the compound showed the NH stretching band at 3160 cm^{-1}, which was consistent with those of II, III, and 2-phenoxy-2-thioxoperhydro-1,3,2-diazaphosphepin.[6,9] These data indicated the compound has undoubtedly the structure I. 2-Phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole 2-oxide I thus synthesized is now soluble in acetone, tetrahydrofuran, and hot benzene. When the compound I was treated with aqueous tetrahydrofuran at room temperature overnight, hydrolysis product (V) as expected was obtained in a good yield. The compound I was also isolated by the careful examination of the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate in refluxing benzene. After the reaction, the precipitate was removed and the benzene solution was concentrated and kept at around 10° to give a trace of the colorless needles, which was identified as I by the comparison of IR and melting point. It appears that although I was formed in refluxing benzene, it was hydrolyzed to V by the Autenrieth and Bolli's work-up procedure. In this respect, Edmundson's suggestion that the cyclic phosphorodiamidate I is not obtained by the reaction of phenyl phosphorodichloridate and *o*-phenylenediamine should be corrected. The further study of the reactions of I and V are now in progress and will be reported elsewhere.

Experimental

Synthesis of Phenyl Phosphorodichloridate——The compound was prepared by the procedure reported by Katyshkina, *et al.*[10] as follows. A mixture of 31 g of phenol, 1.6 g KCl and 183 ml of freshly distilled $POCl_3$ was refluxed for 6.5 hr. After the reaction, the excess $POCl_3$ was distilled off. The residue was distilled under reduced pressure to give 50.3 g (70%) of an oil, bp 133—134°/27 mm. *Anal.* Calcd. for $C_6H_5O_2Cl_2P$: C, 34.17; H, 2.37. Found: C, 34.36; H, 2.47. IR ν_{max}^{liq} cm^{-1}: 3040, 1590, 1495, 1310, 1190, 1170, 960, 780, 700. The purity of the dichloride was confirmed by vaper–phase chromatography (VPC) of the dimethyl ester. 2.11 g of phenyl phosphorodichloridate was dissolved in a mixture of 2.02 g of Et_3N and 40 ml of MeOH. The solution was kept at room temperature overnight and the solvent was evaporated.

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8) R.S. Edmundson, *J. Chem. Soc.* (*C*), **1971**, 3614.

9) *a*) W. Autenrieth and W. Meyer, *Chem. Ber.*, **58**, 848 (1925); *b*) W. Autenrieth and O. Hildebrand, *ibid.*, **31**, 1111 (1898).

10) V.V. Katyshkina and M. Ya. Kraft, *Zhur. Obschei Khim.*, **26**, 3060 (1956).

The residue was extracted with ether and the ether extract was dried with Na_2SO_4 and evaporated to leave 2.2 g of oil, which showed single peak in VPC (10% polyethyleneglycol succinate on Chromosorb W) and was identical with dimethyl phenyl phosphate by the comparison of IR and nuclear magnetic resonance (NMR).

Reaction of *o*-Phenylenediamine with Phenyl Phosphorodichloridate in Refluxing Benzene——To a solution of *o*-phenylenediamine (20 g, 0.185mol) in 200 ml of dry benzene was added dropwise 19.5 g (0.09mol) of phenyl phosphorodichloridate in 100 ml of benzene under stirring. The suspension was stirred for 1 hr at room temperature and was refluxed for 4 hr. The solvent was evaporated *in vacuo* and the residue was washed with water several times. The residue was recrystallized from EtOH–H_2O to give 11.7 g of fine needles, mp 175—177°. *Anal.* Calcd. for $C_{12}H_{13}O_3N_2P \cdot H_2O$: C, 51.11; H, 5.36; N, 9.93. Found: C, 51.20; H, 5.08; N, 9.93. The IR spectrum of the compound and mp was identical with those of phenyl hydrogen N-(2-aminophenyl)phosphoroamidate hydrate reported by Edmundson. The compound lost water after drying 23 hr at 100° to give a crystalline compound of mp 162—163°. *Anal.* Calcd. for $C_{12}H_{13}O_3N_2P$: C, 54.59; H, 4.96; N, 10.61. Found: C, 54.38; H, 5.02; N, 10.44. The monohydrate is insoluble in benzene, $CHCl_3$, AcOEt, cold EtOH, and cold H_2O. It is soluble in hot EtOH and hot H_2O.

Reaction of Phenyl Hydrogen N-(2-Aminophenyl)phosphoroamidate (V)——Hydrolysis of V: Four hundreds ninetytwo milligrams of V was suspended in 50 ml of H_2O and heated at 100—110°. After 10 min, a clear solution was obtained. After refluxing for 16 hr, the solution was extracted with ether and the ether solution was washed with H_2O and dried with Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography to give 52 mg of the crystals, mp 35—37°, which was identified as phenol by IR and mixed melting point. The aqueous layer was evaporated to dryness and the residue was recrystallized from EtOH to give 124 mg of colorless needles, mp 169—171°. *Anal.* Calcd. for $C_6H_{11}O_4N_2P$: C, 34.98; H, 5.38; N, 13.60. Found: C, 34.78; H, 5.31; N, 13.50. IR ν_{max}^{KBr} cm^{-1}: 3300, 3200, 3100—2000 (broad), 1640, 1550, 1270, 1220, 1130, 1030, 970, 840, 760. The compound was identified as *o*-phenylenediamine dihydrogenphosphate by the comparison of IR and mixed melting point determination with an authentic sample.

Acid-catalyzed Hydrolysis of V: A solution of V (1.2 g) in 70 ml of 1N HCl was refluxed for 6.5 hr and the solvent was evaporated to dryness *in vacuo*. The residue was extracted with ether to give 877 mg of an oil. Crystallization from $CHCl_3$ gave 320 mg of needles, mp 94—96°. IR ν_{max}^{KBr} cm^{-1}: 3600—2000 (broad), 1595, 1490, 1225, 1170, 1120—970 (broad). The compound was identified as phenyl phosphate by the comparison of IR and mixed melting point with those of an authentic specimen. The aqueous layer was evaporated to dryness and the residue (770 mg) was recrystallized from EtOH to give 626 mg of needles, mp 204—205°, IR ν_{max}^{KBr} cm^{-1}: 2800, 2560, 1585, 1525, 1495, 1150, 765. The compound was identified as *o*-phenylenediamine dihydrochloride by the comparison of IR and mixed melting point.

Methanolysis of V: A solution of V (1.7 g) in 150 ml of abs. MeOH was refluxed for 24 hr and the solution was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 1.47 g of *o*-phenylenediamine salt of methyl phenylphosphate as plates, mp 155—157°. *Anal.* Calcd. for $C_{13}H_{17}O_4N_2P$: C, 52.57; H, 5.79; N, 9.46. Found: C, 52.60; H, 5.82; N, 9.56. IR ν_{max}^{KBr} cm^{-1}: 3400, 3240, 2880, 2600, 1225, 1085, 1060. A part of the product was dissolved in dil. HCl and the solvent was evaporated. The residue was extracted with ether. The ether solution was dried with Na_2SO_4 and cyclohexylamine was added to the ether solution to give white crystals, which was recrystallized from acetone–$CHCl_3$ to give cyclohexylammonium methylphenylphosphate as needles, mp 149—151° (lit.[11] 150—152°). *Anal.* Calcd. for $C_{13}H_{22}O_4NP$: C, 54.40; H, 7.73; N, 4.88. Found: C, 54.31; H, 7.47; N, 4.85.

Fusion of *o*-Phenylenediamine with Phenyl Phosphorodichloridate——To 5.8 g of *o*-phenylenediamine (54 mM) was added 5.6 g of phenyl phosphorodichloridate (26.5 mM). An exothermic reaction occurred and HCl gas evolved. The mixture was heated to 170—180° for 2.5 hr to give a pale green syrup. After washing with H_2O several times, the residue was fractionally recrystallized from EtOH–H_2O to give 1.5 g of V and 1.74 g of VI as needles, mp 183—184°. *Anal.* Calcd. for $C_{18}H_{19}O_4N_2P$: C, 60.39; H, 5.35; N, 7.83. Found: C, 60.39; H, 5.25; N, 7.89. IR ν_{max}^{KBr} cm^{-1}: 3460, 3320, 3000—2500 (broad), 1230, 1210, 1080. The compound VI was identified as *o*-phenylenediamine salt of diphenyl phosphate by comparing the IR spectrum and mp with the authentic specimen, which was prepared by the reaction of *o*-phenylenediamine with diphenyl phosphate.

Reaction of *o*-Phenylenediamine Salt of Diphenyl Phosphate (VI)——Recovered Reactions: VI was recovered unchanged under the following reaction conditions.

1) H_2O: 24 hr reflux
2) abs. MeOH: 24 hr reflux
3) NH_4Cl–H_2O (200 mg/50 ml) : 24 hr reflux
4) 10% AcOH–H_2O : 7.5 hr reflux

Acid-catalyzed Hydrolysis of VI: A mixture of 1 g of VI and 50 ml of 1N HCl was refluxed for 16 hr. The reaction mixture was extracted with ether. To the dried ether solution was added cyclohexylamine

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11) F. Cramer and G. Weimann, *Chem. Ber.*, **94**, 996 (1961).

to give 250 mg of needles, mp 197—198°, which was identical with standard cyclohexylammonium diphenyl phosphate, mp 195—196° (lit.[12] 200—201°). The aqueous layer was evaporated to dryness and was extracted with $CHCl_3$. The $CHCl_3$ extract was dissolved in ether and cyclohexylamine was added to give 190 mg of needles, mp 203—204°, which was identical with standard biscyclohexylammonium phenylphosphate, mp 203—204° (lit.[13] 214—215°). The residue was recrystallized from EtOH to give 510 mg of *o*-phenylenediamine dihydrochloride, mp 199—201°.

Synthesis of 2-Phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole 2-Oxide (I)——i) Reaction of *o*-Phenylenediamine with Phenyl Phosphorodichloridate in Bromobenzene: To a solution of 4.32 g of *o*-phenylenediamine (40 mM) in 60 ml of dry bromobenzene was added 8.44 g of phenyl phosphorodichloridate (40 mM) in 10 ml of dry bromobenzene under stirring at room temperature. During the addition precipitate was formed. The suspension was refluxed and evolved HCl gas was trapped with H_2O and titrated with 0.1N NaOH. Refluxing was continued until theoretical amount of HCl was evolved (2.5 hr). After the solution was cooled, 1.7 g of the unidentified precipitate of mp 243—248°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3040, 1615, 1495, 1420, 1310, 1250, 1115, 1040, 750, was removed and the bromobenzene solution was kept in a refrigerator to give 1.42 g of needles, mp 151—153°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2P$: C, 58.59; H, 4.51; N, 11.39. Found: C, 58.64; H, 4.46; N, 11.64. IR $_{\max}^{\text{KBr}}$ cm^{-1}: 3160, 1600, 1495, 1405, 1300, 1200, 960. Mass Spectrum *m/e*: 246 (M^+), 153 ($M^+-C_6H_5O$), 108 ($C_6H_8N_2$), 94 (C_6H_6O).

ii) Reaction of *o*-Phenylenediamine with Phenyl Phosphorodichloridate in Refluxing Benzene: To a solution of 10.8 g of *o*-phenylenediamine (0.1 mole) in 200 ml of dry benzene was added 10.5 g of phenyl phosphorodichloridate (0.05 mole) in 10 ml of dry benzene under stirring. The suspension was kept at room temperature for 1 hr and then refluxed for 4 hr. After leaving the solution at room temperature for half an hour, the solid was removed by centrifugation and the solution was kept at 5—10° overnight to give 320 mg of needles, mp 155°, which was identical with that obtained by the reaction in bromobenzene by the comparison of IR and mixed mp.

Hydrolysis of 2-Phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole 2-Oxide (I)——To a solution of 246 mg of I in 10 ml of tetrahydrofuran and 10 ml of H_2O was kept at room temperature for 6 hr and the solvent was evaporated to dryness *in vacuo* to give 300 mg of the crude product, whose IR spectrum was identical with V. It was recrystallized from H_2O to give 105 mg of needles, which was identical with V by the comparison of IR and mixed mp.

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12) J. Lecocq and A.R. Todd, *J. Chem. Soc.*, **1954**, 2381.

13) J. Baddiley, V.M. Clark, J. Michalski, and A.R. Todd, *J. Chem. Soc.*, **1949**, 815.