# Imidazolylphosphonamidochloridothionates

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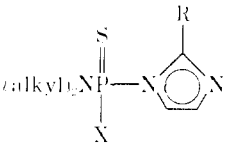
The synthesis, chemical behavior, and biological activity of N,N-dialkyl imidazol-1-ylphosphonamidochloridothionates, a novel type of organophosphoramide compound, have been studied. These compounds possess a marked intrinsic nucleophilicity which depends strongly on the geometry of the individual compounds. This feature gives rise to several new reactions and novel types of structure which have been investigated in some detail. The profile of biological activity of the compounds involved is discussed briefly.

In the course of our work on biologically active phosphorus derivatives of imidazole[1] we recently described the biological and chemical aspects of imidazolylphosphinamidothionates[2a] and the resolution of certain asymmetrically structured members of this type of compound.[2b] These phosphinamidothionates had structure I and were closely related to imidazol-1-ylphosphonamidochloridothionates (II).



I, X = hydrocarbyl; R = H or Me
II, X = Cl; R = H or Et

Since compounds II represented a novel class of compound containing two fundamentally different leaving groups, Cl and imidazole, at the central P atom, we studied the biological as well as the chemical aspects of the new compounds.

**Biological Aspects.**—Compounds of structure II were investigated as to their fungicidal activity against powdery mildew and late blight (Table I). The fungicidal data listed were minimum concentrations of racemic I and II in parts per million of aqueous formulation required to produce complete control of the two plant diseases mentioned.

TABLE I
FUNGICIDAL ACTIVITY OF I AND II (R = H)

| Alkyl | X | Powdery mildew, ppm | Late blight, ppm |
|---|---|---|---|
| Me | Cl | >150 | >150 |
| | Ph | >150 | 9 |
| Et | Cl | >150 | ~150 |
| | Ph | 10 | 18 |
| Pr | Cl | <150 | >150 |
| | Ph | 37 | >150 |
| $-(CH_2)_5-$ | Cl | >150 | >150 |
| | Ph | 9 | >150 |

We have previously reported that for maximum fungal toxicity X evidently has to be planar and mildly electron attracting.[2a] The data given in Table I are in accord with this generalization to the extent that a strongly electron-attracting substituent in place of X should cause a reduction in fungicidal activity. We have also pointed out that compounds I (X = Ph, R = H) tend to have only moderate mammalian toxicity.[1,2a] Apparently, a Cl atom in place of Ph (II, X = Cl, R = H) does not change this trend substantially. For instance, IIa (X = Cl, R = H, alkyl = Me) has an acute oral $LD_{50}$ of ~750 mg/kg in rats, while the corresponding value for Ia (X = Ph, R = H, alkyl = Me) is about 1500 mg/kg.[3]

**Chemical Aspects.**—As to structure II we expected its P atom to be moderately electrophilic and its S as well as azole N to be markedly nucleophilic.[4] In order to investigate this situation experimentally we prepared the N,N-dialkyl imidazol-1-ylphosphonamidochloridothionates (II) from N,N-dialkyl phosphoramidodichloridothionates (III) and imidazoles (R = H or Et) in the presence of triethylamine at the theoretical mole ratio of 1:1:1. Crude II was obtained in yields of better than 80% and in purities above 95%. Purification of II by molecular distillation gave an unexpected result. The distillate was found to contain not only II but also III and N,N-dialkyl diimidazol-1-ylphosphinamidothionates (IV), in the proportions given in Table II.

TABLE II
PRODUCTS OBTAINED FROM DISTILLATION OF CRUDE II

| Compd II | Alkyl | R | Yields,[a] % II | III | IV |
|---|---|---|---|---|---|
| a | Me | H | 30.0 | 93.6 | 42.6 |
| b | Et | H | 46.3 | 89.2 | 52.9 |
| c | *n*-Pr | H | 50.0 | 90.8 | 12.3 |
| d | *i*-Pr | H | 53.3 | | |
| e | $-(CH_2)_5-$ | H | 32.4 | 85.6 | 63.8 |
| f | Me | Et | 71.0 | 79.4 | 76.0 |
| g | Et | Et | 75.2 | 88.2 | 15.6 |
| h | *n*-Pr | Et | 76.6 | 77.3 | 6.8 |
| i | *i*-Pr | Et | | | |

[a] Yield is per cent of theory based on reaction a.

The data in Table II revealed that during the distillation, *i.e.*, exposure of II to elevated temperature, maximum quantities of III and IV were formed if the number of carbon atoms in R and the alkyl groups of II was at minimum. Increasing size and shape of these groups reduced the yields of III and IV. Formation of these

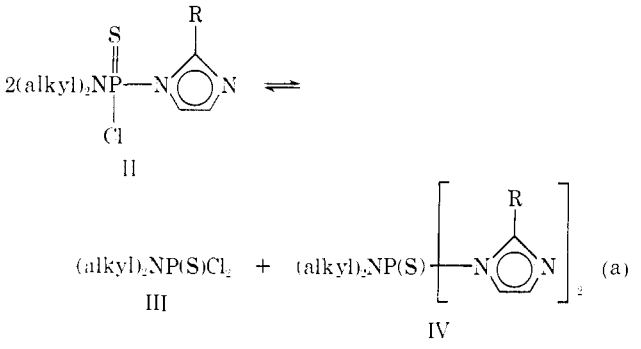
(1) (a) H. Tolkmith, D. N. Saiber, P. B. Budde, and D. R. Mussell, *Science*, **158**, 1462 (1967); (b) H. Tolkmith and D. R. Mussell, *World Rev. Pest Control*, **6**, 74 (1967).

(2) (a) H. Tolkmith, P. B. Budde, D. R. Mussell, and R. A. Nyquist, *J. Med. Chem.*, **10**, 1074 (1967); (b) J. N. Seiber and H. Tolkmith, *Tetrahedron Letters*, 3333 (1967).

(3) In a homologous series of I (X = Ph, R = H; alkyl = Me, Et, *i*-Pr) the acute oral $LD_{50}$ on rats has values of ~1500, ~1000, and ~625 mg/kg, respectively. Thus, the mammalian toxicity increases with decreasing phosphorylation ability and is not accounted for merely by anticholinesterase activity.

(4) *Cf.* ref 2b.

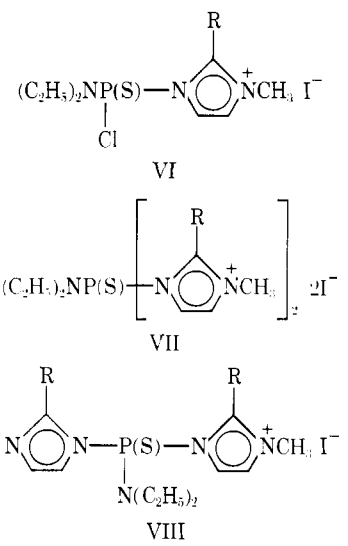
products was completely suppressed if the alkyl groups at the amido N were at least as bulky as *i*-Pr. The same observations were made if distilled II was redistilled. These findings clearly indicated that compounds II underwent the following disproportionation reaction (a) and that the extent of occurrence of this reaction was controlled by the size and shape of the groups in place of alkyl and R.[5]



The noteworthy feature of observation was not so much the fact that a disproportionation reaction occurred in the first place but that this reaction took place already at 80–100°. Thermal disproportionations of thionophosphoryl chlorides containing asymmetric P are a well-known phenomenon but usually require temperatures of about 150°.[6] Possibly, the new reaction (a) could involve the initial formation of $Cl^-$ and imidazolyl, leading to a redistribution of these groups at P. In a more attractive alternative the initial step could be an attack of the rather strongly nucleophilic azole N of one molecule of II on a somewhat electrophilic P atom of another molecule of II, leading to the liberation of $Cl^-$ and subsequent formation of III and IV.

In order to test this hypothesis we studied the nucleophilicity of II toward C in MeI. Using IIb and its 2-Et homolog (IIg) as representative nucleophilic reagents we found that IIg smoothly produced the expected derivative of structure VI (R = Et) in near quantitative yield. The nmr spectrum of the reaction product clearly revealed that it was the azole N and not the S in IIg which had been methylated.[7] An analogous reaction of IIb with MeI did not provide the expected homolog of structure VI (R = H). The main product actually isolated from this reaction was found to have structure VII (R = H).

At first sight it might appear unusual that two homologous species of II should behave so differently in their reaction with MeI. However, the unexpected formation of VII (R = H) could have occurred in the following manner. If the electron deficiency of P in VI (R = H) is similar to the electron deficiency of C in MeI the nucleophilic IIb will react not only with MeI but also with VI (R = H). Reaction with the latter would produce III (alkyl = Et) and the novel structure VIII (R = H). This compound will react with MeI to afford the new structure VII (R = H). We proved the existence of VIIIa (R = H) and VIIIb (R = Et) by methylating IVb (alkyl = ethyl, R = H) and IVg (alkyl = Et, R = Et) under mild conditions. Thus, the over-all reaction of compounds of the novel structure II with excess MeI











may proceed as shown if alkyl is ethyl. This sequence of reactions apparently is arrested at stage VI if R is Et but proceeds to stage VII if R is H. We interpret this phenomenon by assuming that the nucleophilic attack of II on VII is sterically affected by the size and shape of R, unless this substituent is H. The same interpretation can serve to explain the results of reaction a. An ionic dissociation–recombination mechanism may be conceivable for reaction a but would be of no help in regard to the reaction involved in b.

The discovery of the reaction II + MeI → VI suggested that racemic II might be resolved by treating it with the Me ester of an optically active acid, *e.g.*, *α-d*-camphorsulfonic acid. This novel method of resolving asymmetric organophosphoramides was developed in our laboratory for compounds of structure I (X = Ph, R = Me, alkyl = Et).[2b] It did not prove successful in the case of II. The diastereomeric complex was found to degrade too rapidly to permit resolution.

## Experimental Section[8]

For ir analyses, a Beckman IR-9 filter-grating spectrometer over the 3800–400-$cm^{-1}$ region was employed. Spectra of 10% solution of the compounds in $CCl_4$ (for the 3800–1333-$cm^{-1}$ region) and in $CS_2$ (for the 1333–400-$cm^{-1}$ region) were scanned using 0.1-mm KBr cells. For nmr analyses, a Varian A-60 instrument and 20% solutions of compounds in $CDCl_3$ were used. The characteristic ir frequencies ($cm^{-1}$) and chemical shifts relative to TMS for the imidazol-**1**-yl protons used for identification purposes have been reported previously.[2] The melting points are uncorrected and have been determined according to Berhenke.[9]

**N,N-Dialkylimidazol-1-ylphosphonamidochloridothionates** (II) were prepared by the dropwise addition of a solution of imidazole (0.5 mole) and $Et_3N$ (0.55 mole) in 1,2-dimethoxyethane (~200 ml) to an agitated solution of the appropriate N,N-dialkyl

(5) The yields given in Tables II for III are data of recovery and not of formation since the high vacuum applied prevented complete recovery of III as formed.

(6) L. C. D. Groenweghe, L. Mayer, and H. E. Ulmer, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p M-18.

(7) *Cf.* ref 2b.

(8) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(9) L. F. Berhenke, *Anal. Chem.*, **33**, 65 (1961).

TABLE III

ANALYTICAL AND PHYSICAL DATA OF IIa–i

| Compd II | Formula | Analyses | Bp, °C (μ) | $d_{25}$ | $n_{25}D$ |
|---|---|---|---|---|---|
| a | $C_5H_9ClN_3PS$ | H, N, Cl; C[a] | 55–57 (20) | 1.324 | 1.5646 |
| b | $C_7H_{13}ClN_3PS$ | H, N; C, Cl[b] | 85–87 (30) | 1.223 | 1.5443 |
| c | $C_6H_{17}ClN_3PS$ | C, H, Cl; N[c] | 94–95 (0.1) | 1.178 | 1.5415 |
| d | $C_9H_{17}ClN_3PS$ | C, H, N; Cl[d] | 83–85 (0.8) | | |
| e | $C_8H_{13}ClN_3PS$ | C, H, N; Cl[e] | 80 (0.2) | | |
| f | $C_7H_{13}ClN_3PS$ | C, H, Cl, N | 63 (0.2) | 1.250 | 1.5551 |
| g | $C_9H_{17}ClN_3PS$ | C, H, Cl, N | 75 (0.2) | 1.193 | 1.5445 |
| h | $C_{11}H_{21}ClN_3PS$ | C, H, Cl, N | 71 (0.2) | 1.140 | 1.5345 |
| i | $C_{11}H_{21}ClN_3PS$ | C, H, Cl, N | | | |

[a] C: calcd, 28.63; found, 29.20. [b] C: calcd, 35.80; found, 35.38. Cl: calcd 14.92; found, 14.50. [c] N: calcd, 15.80; found, 15.00. [d] Cl: calcd, 13.30; found, 12.80. [e] Cl: calcd, 14.40; found, 13.90.

phosphoramidodichloridothionate (0.5 mole) in the same diluent (~200 ml) at 0–5° over a 1–4-hr period. The resulting mixture was stirred at 0–5° for ~18.0 hr and diluted with 250 ml of 1,2-dimethoxyethane, the insoluble $Et_3NH^+Cl^-$ was filtered, and the diluent was removed from the filtrate by evaporation. The residue was taken up in $CCl_4$ (250 ml), the insolubles were filtered, and the solvent was evaporated from the filtrate. The resulting residue was treated in a similar manner with hexane. The crudes thus obtained represented the following compounds (yields in per cent of theory given in parentheses): IIa (90.4), IIb (84.0), IIc (88.2), IId (60.5), and IIe (quantitative). In the preparation of IId the reaction mixture had to be refluxed for 18.0 hr to ensure a good reaction. Distillation of the crude product gave a 53.3% yield; the distillate crystallized on standing (mp 46°). Molecular distillation of the other crudes of structure II gave products of disproportionation as shown in Table II. Combustion data of crude IIa–e and physical data after distillation were found to be as given in Table III.

The 2-ethylimidazol-1-yl homologs were prepared in an analogous manner. The main alteration of the above procedure was reaction temperature. IIf and IIg were synthesized at room temperature, while IIh required refluxing. Yields of the crude reaction products were as follows: IIf (91.3), IIg (91.6), and IIh (90.5). Distillation of these crudes gave the products shown in Table II. Refluxing equivalent molar amounts of 2-ethylimidazole, N,N-diisopropyl phosphonamidodichloridothionate, and $Et_3N$ in 1,2-dimethoxyethane for 40.0 hr gave a 49.0% yield of IIi (mp 124–126°, from 1,2-dimethoxyethane). Combustion data of crude IIf–i and physical data after distillation were as given in Table III. The structure of these compounds was in accord with recently established ir and nmr standards.[2]

**N,N-Dialkyl Diimidazol-1-ylphosphinamidothionates (IV).**—Compounds of this structure as obtained in the molecular distillation of crude II were found to have satisfactory combustion data. Their identity was demonstrated also on the basis of ir and nmr standards recently reported by us.[2] A synthesis of IIb from the corresponding III and imidazole at the molar ratio of 1:2 was reported previously.[2a] Distilled IV showed the physical data listed in Table IV.

**N,N-Dialkyl Phosphoramidodichloridothionates (III).**—This type of compound as well as the compounds indicated in Table II are well known in the literature.[10] They were identified by means of known ir standards.[4]

(10) K. Sasse in "Methoden der Organischen Chemie," Vol. XII/2, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1964, p 750.

TABLE IV

PHYSICAL DATA OF IV

| Compd IV | Mp, °C | Bp, °C (μ) |
|---|---|---|
| a | | 99 (2) |
| b | 40 | 117 (0.1) |
| c | | 131 (0.1) |
| e | 80 | |
| f | 77–78 | 82 (0.2) |
| g | 56–58 | 95 (0.1) |
| h | 79 | |

**Reaction of II with MeI.**—A mixture of IIb (0.1 mole) and MeI (1.0 mole) were agitated and refluxed for 14.0 hr. Then, 1,2-dimethoxyethane (100 ml) was added to the reaction mixture, and the insoluble product VII (R = H) was filtered and dried under vacuum; yield 21.7%, mp 154–155°. Under the same reaction conditions IIg afforded VI (R = Et), yield 90.2%, mp 143–145°. Structures were confirmed by ir and nmr analyses.[2]

*Anal.* ($C_{12}H_{22}I_2N_3PS$, VII): H, I; C: calcd, 26.08; found, 25.54. N: calcd, 12.65; found, 12.10. ($C_{16}H_{20}ClIN_3PS$, VI): C, H, N; Cl: calcd, 8.70; found, 8.20. I: calcd, 31.10; found, 31.60.

**Preparation of VIIIa and VIIIb.**—MeI (1.0 mole) and N,N-diethyl diimidazol-1-ylphosphinamidothionate (0.1 mole) were stirred 0–5° for 20.0 hr. The reaction mixture was diluted with 1,2-dimethoxyethane (250 ml) and stirred at 0–5° for 1.0 hr. The insoluble VIIIa (R = H) was filtered and dried; yield 54.5%, mp 134–137°. Similarly prepared was VIIIb (R = Et): yield 61.6%, mp 129–132°. The structures of VIIIa and VIIIb were confirmed by ir and nmr analyses.

*Anal.* Calcd for $C_{11}H_{19}IN_5PS$ (VIIIa): C, 32.12; H, 4.63; N, 17.03; I, 30.86. Found: C, 31.70; H, 4.74; N, 16.50; I, 30.10. Calcd for $C_{15}H_{23}IN_5PS$ (VIIIb): C, 38.55; H, 5.82; N, 14.94; I, 27.14. Found: C, 37.80; H, 5.74; N, 14.70; I, 27.80.

**Acknowledgments.**—The fungicidal data and toxicity data were contributed by D. R. Mussell and Jessica Norris, respectively.