Imidazolylphosphinamidothionates

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The chemical and biological aspects of imidazol-1-ylphenylphosphinamidothionates, a novel type of organophosphoramide, are discussed with particular reference to *N,N*-diethylimidazol-1-ylphenylphosphinamidothionate, an outstanding fungicide of low, acute mammalian toxicity and remarkable stability to nonenzymatic solvolysis. Experimental evidence pertaining to the mechanism of its biological action indicates that this mechanism apparently is different from the mode of action of insecticidal and mammalicidal organophosphorus compounds.

In our more recent work on biologically active organophosphoramides we discovered that *O,O*-dialkyl phthalimidophosphonothionates showed a rather unique combination of biological properties.[1] This finding prompted certain theoretical speculations that led to an investigation of a variety of imidazole derivatives.[2] Among these the imidazol-1-ylphosphinamidothionates were found to possess certain, noteworthy biological and chemical features which we should like to describe. The compounds in question had the novel structure I (see Table I).

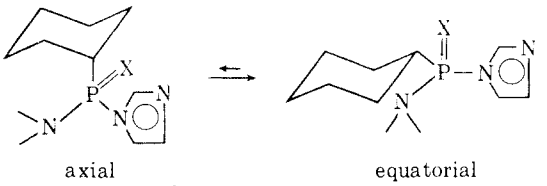
Biological Aspects.—The change of biological activity with the structure of this type of asymmetric phosphorus compound was as given in Table I. The fungicidal data listed were minimum concentrations of racemate in parts per million of aqueous formulation required to produce complete control of the two plant diseases, powdery mildew and late blight. These data clearly revealed the outstanding activity of Ib and the following details concerning relationships between biological activity and molecular structure.

The presence of sulfur as X evidently was critical for good fungicidal activity as revealed by a comparison of Ib with Ih and If with Ii. The same structural characteristic was found with the mentioned fungicides, the *O,O*-dialkyl phthalimidophosphonothionates.[1]

The effect of the alkyl groups at nitrogen was similar to the effect of the alkyl groups in phthalimidophosphonothionate diesters.[1b] For alkyl groups containing unbranched carbon chains of less than five C atoms the activity was maximum with ethyl groups in imidazol-1-ylphosphinamidothionates and with ethyl or propyl groups in phthalimidophosphonothionates.

A more intriguing effect was produced by varying the structure of R. Replacement of the phenyl group of Ib by another, planar, aromatic group, *e.g.*, by a second imidazolyl group, resulted in a marked decrease in the degree of activity against both diseases. The same effect was observed with a β-styryl group or a phenoxyl group as R in Ib. Since phenyl, β-styryl, and phenoxyl substituents had Taft's σ^* values of +0.6, +0.41, and +2.38, respectively, there evidently was no linear relationship between the inductive effect of R and the fungicidal activity of I. Such a relationship is known to exist between the structure and anticholinergic activity of organophosphate esters.[3]

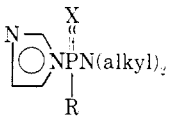
For these reasons we decided to introduce nonplanar hydrocarbon moieties in place of R in I. A methyl group introduced in this manner was found to give only low fungicidal activity. The presence of a cyclohexyl group, however, caused a drastic reduction in the activity against late blight (compare Ia → Ie and Ib → If), while the control of powdery mildew was not seriously affected. The presence of a piperidyl group (compare Id → Ig) gave a similar result. Compounds Ie, If, and Ii probably contained two, conformationally different isomers of which the equatorial form was likely to be very predominant.[4]



Ie, If, and Ii

Thus, the structure of R in I was found to have a relatively small effect upon the activity against powdery mildew and a rather strong influence on the control of late blight. The changes in activity observed by

Table I
Structure and Properties of Imidazolylphosphinamidothionates and -amidates



Compd	R	X	Alkyl	Mp, °C	Min concn, ppm, for complete control: Powdery mildew	Late blight
a	C_6H_5	S	CH_3	Oil	>150	9
b	C_6H_5	S	C_2H_5	43	10	18
c	C_6H_5	S	*n*-C_4H_9	Oil	75	75
d		S	C_2H_5	30–40	75	75
e	C_6H_{11}	S	CH_3	53–56	>150	>150
f	C_6H_{11}	S	C_2H_5	82–3	18	>150
g	$(CH_2)_5N$	S	C_2H_5	48–49	75	>150
h	C_6H_5	O	C_2H_5	55–57	>150	>150
i	C_6H_{11}	O	C_2H_5	65–67	>150	>150

(1) (a) H. Tolkmith, *Nature*, **211**, 522 (1966); (b) H. Tolkmith, H. O. Senkbeil, and D. R. Mussell, *Science*, **115**, 85 (1967); (c) H. Tolkmith and H. O. Senkbeil, Belgian Patent 661,891 (1965).

(2) P. B. Budde and H. Tolkmith, Belgian Patent 680,293 (1966).

(3) D. F. Heath, "Organophosphorus Poisons," Pergamon Press Inc., New York, N. Y., 1961, Chapter IV.

(4) (a) See E. L. Eliel and M. Knoeber, *J. Am. Chem. Soc.*, **82**, 1367 (1960); (b) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 753 (1966).

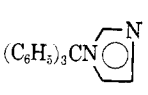
comparing Ia with Ie, Ib with If, and Id with Ig indicated that the shape of the site of toxic action in fungi that cause late blight might be different from the shape of this site in fungi that produce powdery mildew. For maximum toxicity against both types of fungi the R substituent evidently had to be planar and weakly electron attracting, as in Ib.

According to these findings the influence of the polar and steric characteristics of R upon the fungicidal activity of I was more complex than in the familiar case of anticholinergic organophosphates. Therefore, it was conceivable that the mechanism of fungicidal action of I might not even involve phosphorylation of an enzyme essential to the normal functioning of the fungus organism. This hypothesis was supported by the following chemical and biological evidence.

A study of the solvolysis of Ib gave the results shown in Table II. They clearly indicate that the imidazolyl group on Ib is a poor leaving group in the presence of a 4 *M* excess of solvolysis agent.

Compounds Ia, Ib, and Ih were found to have remarkably low insecticidal activity, and their mammalian toxicity, in terms of LD_{50} in milligrams per kilogram orally on rats, had values of about 1500, 1000, and 750, respectively. This evidence implied that the compounds were not particularly effective phosphorylating agents of cholinesterases *in vivo*. In agreement with this assumption, Ib and Ih were found to show very low anticholinergic activity.

The strongest support for the hypothesis proposed was provided by the finding that fungicidal potency was not affected if the entire phosphorus group, $RP(X)N(alkyl)_2$, in compounds of structure I was replaced by a phosphorus-free substituent of suitable, stereoelectronic character. It was found that 1-tritylimidazole gave complete control of powdery mildew and late blight at concentrations of, respectively, 10 and 35 ppm.[5,6]



(5) D. R. Mussell and H. Tolkmith, U. S. Patent application (allowed).

(6) On the basis of the evidence described in this paper it is clear that the fungicidal activity of compounds of structure I is not critically dependent upon their phosphorylation ability. More likely, their activity may arise from the fact that they are imidazole derivatives. Thus, I may react *in vivo* by a mechanism similar to the well-known mechanism of imidazole itself.[7a] While compounds of structure I are theoretically capable of functioning as ambident nucleophiles, it is known that the nucleophilicity of sulfur at phosphorus in phosphoramidothionates can easily be blocked by steric factors.[7b] In fact, the S atom in Ib cannot be alkylated by reaction with primary alkyl halides. As a result, the compound Ib and 1-tritylimidazole have in common the presence of only one nucleophilic atom, the azole nitrogen of the imidazole ring. This feature and the similarity between the stereoelectronic character of the trityl group and the phosphinamidothionate group in Ib may be related to the fact that Ib and 1-tritylimidazole are nearly equal in the scope and degree of their fungicidal activity. In view of this situation it is postulated that the mechanism of fungicidal action of I differs not only from the well-known mechanism of action of organophosphoramide insecticides[3] but also from the proposed mechanism of action of O,O-dialkyl phthalimidophosphorothionate fungicides.[1a,b] The lack of fungicidal activity found with imidazolylphosphinamidates, such as Ih and Ii, does not seem to result from a reduction in the nucleophilicity of the imidazolyl group because it is well known that the energy of the highest filled molecular orbital has the same value for various types of biologically important imidazole derivatives.[7c] More likely, the lack of activity of the phosphinamidates mentioned may arise from the well-known solvolytic instability of imidazolyl P(O)< groups.

(7) (a) See E. A. Barnard and W. D. Stein, *Advan. Enzymol.*, **20**, 51 (1958); (b) H. Tolkmith, *J. Am. Chem. Soc.*, **85**, 3246 (1963); (c) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963, appendix.

TABLE II
HALF-LIFE TIME ($T_{1/2}$) OF Ib IN SOLVOLYTIC MEDIA

Medium	Temp, °C	$T_{1/2}$, days
n-$C_4H_9NH_2$	75	≫2
C_2H_5OH	75	≫2
H_2O[a]	20	≫30
H_2O[a]	80	<0.5

[a] Homogeneous reaction mixture in dimethoxyethane.

TABLE III
CHLORIDO INTERMEDIATES (II) USED IN THE PREPARATION OF COMPOUNDS OF STRUCTURE I

$$ClP(X)N(alkyl)_2$$
$$|$$
$$R$$

Compd II	R	X	Alkyl	Mp, °C	Bp, °C (mm)	$n^{25}D$	$n^{25}D$
a	C_6H_5	S	CH_3		105 (0.1)	1.228	1.6007
b	C_6H_5	S	C_2H_5	43	137 (0.7)		
c	C_6H_5	S	n-C_4H_9		165 (0.1)	1.096	1.5538
d	Cl	S	C_2H_5	*a*			
e	C_6H_{11}	S	CH_3	73			
f	C_6H_{11}	S	C_2H_5		118 (0.6)	1.1146	1.5346
g	$(CH_2)_5N$	S	C_2H_5		104 (0.2)	1.134	1.5301
h	C_6H_5	O	C_2H_5		132 (0.5)	1.217	1.5243
i	C_6H_{11}	O	C_2H_5	52			

[a] Described by A. Michaelis, *Ann.*, **326**, 201 (1903).

Chemical Aspects.—The compounds listed in Table I were prepared by the reaction of imidazole with chlorido intermediates, $ClP(=X)(R)N(alkyl)_2$ (II), as described in the Experimental Section. Structural details and physical data of these intermediates were as given in Table III.

The chemistry of compounds of structure II has not been studied extensively in the past although they can easily be obtained by the reaction of the known dichlorides, $RP(X)Cl_2$, with appropriate amines. From evidence described with similar reactions,[8] one might expect the mole ratio and mode of addition of the reactants to be critical if a formation of N,N′-tetralkyl diamide is to be prevented. We have found this to be true to a limited extent only. For instance, the reaction of $RP(X)Cl_2$ with dialkylamines at a mole ratio of 1:4 produces II without formation of diamide if R has the shape of a puckered, six-membered ring and if the alkyl group contains at least two carbon atoms, as in the compounds, IIf, IIg, and IIi.

In contrast, if R is a planar, six-membered ring the reaction products formed depend upon the size of the alkyl groups in the dialkylamine involved. As an example, with phenyl in place of R, diethylamine yields a mixture of IIb and the corresponding diamide while di-*n*-butylamine exclusively produces IIc. Thus, nucleophilic displacements of chlorine on phosphorus in II by dialkylamines are controlled also by the steric characteristics of R and alkyl and do not depend merely on the degree of electron deficiency of the phosphorus atom.

From these findings it became evident that certain compounds of structure I, such as Ic, If, Ig, and Ii, could be prepared in a simplified manner based upon the novel reaction 1.

(8) (a) E. H. Blair and H. Tolkmith, *J. Org. Chem.*, **25**, 1020 (1960); (b) K. Sasse, "Methoden der Organischen Chemie," Vol. XII/1, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1963, pp 526, 591; (c) K. Sasse, *ibid.*, Vol. XI/2, 1964, p 773.

$$RP(X)Cl_2 + HN\langle\!\rangle N + 3HN(alkyl)_2 \xrightarrow{-2(alkyl)_2NH\cdot HCl} I \quad (1)$$

$pK_a = 7.16$ $pK_a > 10.5$

If reaction 1 would depend exclusively upon polar effects, the reaction products should be the corresponding tetralkyldiamides and the hydrochlorides of imidazole and dialkylamine. However, the steric factors of $RP(X)Cl_2$ and dialkylamine can be such as to prevent the unshared electron pair of the pyramidal nitrogen atom in some dialkylamines from engaging the rear of the hybrid orbital of phosphorus involved in the P–Cl bond in II. In contrast, the unshared electron pair on the nitrogen atom in the 3 position of the planar imidazole molecule evidently is capable of engaging this hybrid orbital of the phosphorus atom, although imidazole is a markedly weaker base.

Experimental Section

Melting points as listed in Tables I and III are uncorrected and have been determined according to Berhenke.[9]

For ir analyses, a Beckman IR-9 filter-grating spectrometer over the 3800–400-cm^{-1} region was employed. Spectra of 10% solutions 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-A60 instrument and 20% solutions of compound in $CDCl_3$ were used.

Biological Tests.—Determinations of the acute, oral toxicity of Ia, Ib, and Ih to rats and of the fungicidal activity of Ia–Ii against powdery mildew and late blight were carried out by using conventional procedures. The mammalian data were determined by K. J. Olson of Dow's Biochemical Laboratory.

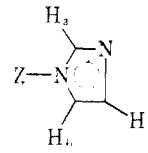
Imadazole compounds of structure I were prepared by dropwise addition of a solution of imidazole (1 mole) and triethylamine (1.1 moles) in 1,2-dimethoxyethane (~600 ml) to a solution of the appropriate intermediate II (1 mole) in the same diluent (300 ml) with agitation at about 25° over a period of 1–4 hr. The resulting reaction mixture was heated for 12 hr at 55–60° and then filtered from the amine hydrochloride formed. Evaporation of diluent from the filtrate and crystallization of the evaporation residue from cyclohexane produced the following compounds (yields in per cent of theory): Ia (87.0), Ie (84.4), If (45.6), and Ii (56.2). Compound Id was obtained in 53.6% yield in the same manner but required the use of 2 moles of imidazole and 2.2 moles of triethylamine per 1 mole of N,N-diethyl phosphoramidodichloridothionate reactant. Reversing the described mode of addition was possible and afforded the compounds Ib (75.6%) and Ih (57.6%). The addition of crystalline imidazole (1 mole) in small portions to a solution of the appropriate intermediate of structure II (1 mole) in triethylamine (6 moles) under the conditions described was another possible modification of the preparation method. In this case the reaction mixture was diluted with benzene or 1,2-dimethoxyethane before it was filtered. The filtrate was worked up as described and provided the compounds Ic (crude yield nearly quantitative) and Ig (65%). The compounds, Ib, Ig, and Ih also were crystallized from cyclohexane. Yield data given for crystalline compounds did not represent maximum yields. With the exception of Ia and Ic, all compounds were isolated as white, crystalline products.

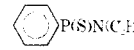
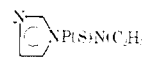
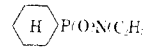
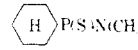
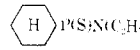
The presence of an imidazole group in Ia–Ii was proved by nmr analysis. The CH protons at the imidazole ring were found to give shift data, relative to TMS, as shown in Table IV. As was to be expected, the protons of the carbon atoms in the 4 and 5 position of the imidazole ring were not equivalent when a phosphorus group was present at the N^1 atom of imidazole. In addition to these analyses, the composition of compounds of structure I was checked also by combustion analysis and ir analysis. The data obtained were as given in Tables V and VI, respectively.

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

TABLE IV

CHEMICAL SHIFTS OF THE CH PROTONS OF THE IMIDAZOLE GROUP



Z	H_a, δ, ppm	H_b, δ, ppm
H	7.73	7.11
 (Ib)	7.80	7.20, 7.03
 (Ih)	7.85	7.21, 7.18
 (Ia)	7.89	7.19, 7.17
 (Ie)	7.95	7.23, 7.13
 (Id)	7.98	7.28, 7.10

Synthesis of I According to Reaction 1.—Dialkylamine (4 moles) was added dropwise at about 25° to an agitated solution of dichloride [1 mole of $RP(X)Cl_2$] in 1,2-dimethoxyethane (~200 ml). The reaction mixture formed was heated for 14 hr at 55–60° with continued agitation and then filtered. The amine hydrochloride isolated was washed with 1,2-dimethoxyethane (~200 ml). Filtrates were combined and agitated; then a solution of imidazole (1 mole) in the same dialkylamine as used before (2 moles) was added. The reaction mixture produced was heated for 14 hr at 55–60° with agitation and filtered thereafter. Evaporation of diluent from the filtrate left a crude product that was shown by ir and nmr analysis to have structure I and not to be the diamidate, $RP(X)[N(alkyl)_2]_2$. Thus, the reaction of phenylphosphonodichloridothionate with di-*n*-buttylamine and imidazole afforded a main product that was structurally identical with Ic. The reactions of cyclohexylphosphonodichloridothionate, cyclohexylphosphonodichloridate, and piperidylphosphonodichloridothionate with diethylamine and imidazole were found to give main products identical with If, Ii, and Ig, respectively. The yield of these three compounds after their crystallization from a benzene–cyclohexane mixture (1:1), from cyclohexane, and from *n*-hexane, respectively, was about one-third higher than the yield obtained from the reactions described in the preceding section.

Phosphonamidochlorides of Structure II.—A mixture consisting of dialkylamine (1 mole) and triethylamine (1.1 moles) was dropwise added at about 25° to an agitated solution of dichloride, $RP(X)Cl_2$ (1 mole) in benzene (200–300 ml). The resulting reaction mixture was heated at 55–60° with agitation for 12 hr and filtered. Evaporation of benzene from the filtrate left a solid or oily residue, depending upon the structure of the compound involved. Crystallization of solid residue from cyclohexane produced the following compounds (yields in per cent of theory): IIb (84.0), IIe (84.4), and IIi (85.7) as white, crystalline substances. Fractionation of oily residue *in vacuo* gave the compounds IIa (64.1), IIc (68.7), IIf (74.5), IIg (78.3), and IIh (57.5) as colorless oils. The identity of IIa–i was established by vapor phase chromatography, ir analysis, and combustion analysis (Tables V and VI).

The novel reaction (1) implied that with certain dichlorides the nucleophilic displacement of chlorine on phosphorus was limited to one chlorine atom only, regardless of the presence of an excess of dialkylamine as the nucleophilic reagent. This aspect was examined in the following manner using diethylamine and di-*n*-butylamine as nucleophiles. The amine (2 moles) was added dropwise at about 25° to an agitated solution (cooling required) of $RP(X)Cl_2$ (0.5 mole) in 1,2-dimethoxyethane (~100 ml). The reaction mixture produced was heated with agitation at 55–60° for 14 hr and then filtered. Diluent was evaporated from the filtrate to obtain the crude main product. This was

TABLE V
COMBUSTION ANALYSIS OF COMPOUNDS I AND II

Compd	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
Ia	$C_{11}H_{14}N_3PS$	52.7	5.6	16.7		52.8	6.0	16.7	
Ib	$C_{13}H_{18}N_3PS$	56.0	6.5	15.1		56.3	6.5	15.3	
Ic	$C_{17}H_{26}N_3PS$	60.9	7.8	12.5		59.9	7.5	12.6	
Id	$C_{10}H_{16}N_5PS$	44.7	6.0	26.0		44.4	6.1	25.7	
Ie	$C_{11}H_{20}N_3PS$	51.5	7.8	16.4		51.7	8.1	16.6	
If	$C_{13}H_{24}N_3PS$	54.7	8.5	14.7		54.9	8.5	14.8	
Ig	$C_{12}H_{23}N_4PS$	50.4	8.0	19.6		50.2	7.6	19.6	
Ih	$C_{13}H_{18}N_3OP$	57.9	6.9	15.9		57.6	6.9	15.6	
Ii	$C_{13}H_{24}N_3OP$	58.0	9.0	15.6		58.0	9.1	15.6	
IIa	$C_8H_{11}ClNPS$			6.3	16.2			6.0	16.1
IIb	$C_{10}H_{15}ClNPS$			5.6	14.3			5.3	14.6
IIc	$C_{14}H_{23}ClNPS$			4.6	11.7			4.8	12.2
IIe	$C_8H_{17}ClNPS$			5.9	15.7			6.2	15.4
IIf	$C_{10}H_{21}ClNPS$			5.5	14.0			5.1	13.7
IIg	$C_9H_{20}ClN_2PS$			11.0	13.9			11.1	13.7
IIh	$C_{10}H_{15}ClNOP$			6.1	15.4			5.8	16.0
IIi	$C_{10}H_{21}ClNOP$			5.8	14.9			5.8	14.1

TABLE VI
CHARACTERISTIC IR FREQUENCIES OF ORGANOPHOSPHORUS GROUPS

Group	Frequency,[l] cm^{-1}
P-Imidazolyl	[3143–3155 w, 3122–3132 w, 3110–3120 w],[a] 1511–1520 w–m, 1100–1114 m,[b] 897–903 w–m, 836–843 w–m, 818–830 w, 648–657 m–s, 615–625 w–m
P-Dimethylamido	[3000–3014 w, 2951–2955 m, 2919–2935 m, 2887–2900 w, 2849–2858 w,[c] 2808–2822 w, 2798–2810 w],[d] 1473–1476 w,[c] 1455–1457 m,[c] 1410–1411 w, 1279–1282 m, 1171–1180 s–m, 1160–1169 m, 975–984 s
P-Diethylamido	[2973–2984 m–s, 2937–2943 m,[c] 2872–2885 w[c]],[a] 1440–1475,[e] 1380–1387 s–m,[f] 1290–1300 w, 1200–1210 m–s, 1151–1168 m–s, 1019–1026 m–s, 940–954 m–s,[g] 920–925 w, 787–797 m
P-Dibutylamido	[2964–2968 vs, 2932–2940 s, 2903–2905 vw, 2878–2879 m–s, 2868–2870 m],[a] 1469 m, 1459–1460 m, 1381–1382 m, 1231 w,[c] 1175–1178 w–m, 1153–1158 m–s to s, 1089–1094 m, 1032–1038 m to s, 990–1000 w–m to m, 924–929 m to m–s, 731–733 m to s
P-Piperidyl	[2980 w,[c] 2940–2944 s, 2895–2902 vw, 2852–2860 m–s],[a] 1466 w,[c] 1454–1455 m, 1443–1446 m, 1370–1374 m,[h] 1328–1335 w to w–m, 1276–1279 w–m, 1201–1202 m–s, 1155–1160 s, 1098–1099 m,[i] 1061–1064 s, 942–958 s, 852–855 w–m, 837–839 w–m, 739–747 s, 541–550 s
P-Phenyl	[3149–3155 w, 3080–3087 w, 3062–3078 w],[a] [1580–1597 w, 1483–1489 w, 1436–1444 m–s, 1304–1311 w, 1103–1110 m–s, 1028–1030 w,[c] 997–1002 w],[j] [741–761 s, 685–693 s][k]
P-Cyclohexyl	[2932–2938 s, 2901–2903 vw, 2851–2858 m–s],[a] 1464–1466 w,[c] 1450–1453 m, 1341–1351 w, 1267–1273 w, 1197–1200 w,[c] 1178–1180 m, 1111–1119 w, 999–1001 w–m, 882–888 w–m, 852–858 m, 823–829 w–m, 514–531 s

[a] C–H stretching. [b] Occurs very near 1103–1110-cm^{-1} band for P-phenyl. [c] Often masked. [d] Bands attributed to CH_3 stretching vibration and to overtone or combination tones in Fermi resonance with CH_3 stretching vibrations. [e] Masked by similar CH_2 deformation of longer alkyl groups. [f] CH_2 wagging. [g] Primarily C–C stretching. [h] Often unresolved from band due to P-diethylamido group. [i] Often unresolved from band due to P-imidazolyl group. [j] In-plane vibrations. [k] Out-of-plane vibrations. [l] w = weak, m = medium, s = strong, w–m = weak–medium, m–s = medium–strong, s–m = strong–medium.

TABLE VII
ΔMR DATA INVOLVING SOME COMPOUNDS OF STRUCTURE II

Compd	ΔMR,[a] cc/mole for D light: Obsd	Theoret[a]
IIc − IIa	88.82 − 61.26 = 27.56	27.88
IIf − IIg	70.84 − 69.41 = 1.43	1.49
IIa − IIh	61.26 − 58.26 = 3.0	3.10

[a] H. Tolkmith, *Ann. N. Y. Acad. Sci.*, **79**, 187 (1959); R. J. W. LeFevre, *Advan. Phys. Org. Chem.*, **3**, 1 (1965).

purified as described below and then identified by ir analysis and vapor phase chromatography, using previously prepared compounds of structure II as standards. The main products formed by the reaction of diethylamine with cyclohexylphosphonodichloridothionate, cyclohexylphosphonodichloridate, and piperidylphosphonodichloridothionate were found to be identical with IIf (bp 117–120° (0.6 mm), 74.5% yield], IIi (mp 50–53°, from hexane, 57% yield), and IIg (80% crude yield), respectively.

The reaction of diethylamine with phenylphosphonodichloridothionate, at a mole ratio of 4:1 under the conditions described, gave a crude main product which was crystallized from hexane. This afforded a crystalline component, identified as IIb by vapor phase chromatography and ir analysis, and left an oily residue, found to consist of 50% IIb and 50% N,N,N′,N′-tetraethylphenylphosphonodiamidothionate (III). According to the weight of the IIb crop and the weight and composition of the oil residue from the crystallization, the reaction of 4 moles of diethylamine with 1 mole of phenylphosphonodichloridothionate produced IIb and III at a mole ratio of 5:1. The analogous reaction of this dichloridothionate with di-*n*-butylamine was found to produce IIc as the only main product (yield, 73.6%), identified by vapor phase chromatography and nmr analysis.

The availablility of data on densities and refractive indices of IIa, IIc, and IIf–h permitted a comparison of observed values for the difference between the Lorenz–Lorentz molar refractions of a given pair of compounds (ΔMR) with theoretical values for such differences. The data given in Table VII showed satisfactory agreement between experimental values and theoretical data.

Dichloride starting products, *i.e.*, cyclohexylphosphonodidichloridate,[10] cyclohexylphosphonodichloridothionate,[11] piperidylphosphonodichloridothionate,[12] and N,N-diethylphosphoramidodichloridothionate[12] were prepared according to the references quoted with them. The two remaining starting products, phenylphosphonodichloridate and phenylphosphonodichloridothionate, were commercially available and were distilled before use.

(10) R. Graf, *Chem. Ber.*, **85**, 9 (1952).
(11) M. I. Kabachnik and N. N. Godovikov, *Dokl. Akad. Nauk SSSR*, **110**, 217 (1956).
(12) Footnote *a*, Table III.