[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

NITROGEN COMPOUNDS OF THE PHOSPHORIC AND PHOSPHONIC ACIDS. I. HYDRAZIDES OF PHENYLPHOSPHORIC AND DIPHENYLPHOSPHORIC ACIDS.

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Considerable interest has been manifested during the past few years in the synthesis of a wide variety of hydrazine derivatives, many of which have been prepared for biological evaluation. The hydrazide function in particular has been shown to possess toxiphoric character. A large number of organophosphorus compounds have also been synthesized and studied following the initial discovery by Schrader (1) that many of these substances possess biological activity. It therefore seemed of interest to give consideration to a study of hydrazine derivatives of the phosphoric and phosphonic acids in the hope that such studies might help to extend our knowledge of the relationship between structure and biological activity.[4] Kosolapoff (2) lists only a limited number of phosphorohydrazidates. Little is revealed in the original literature concerning these substances beyond the preparative methods and a few of the physical properties of typical compounds.

Diphenylphosphorohydrazidate (I), $(C_6H_5O)_2PON_2H_3$, can be prepared in good yield by the hydrazinolysis of the chloridate in alcoholic solution (3). This compound behaves as a typical hydrazide and reacts (a) with carbonyl compounds to yield the corresponding diphenoxyphosphinylhydrazones, (b) with ethyl chloroformate to form an N^2-carbethoxy derivative, and (c) with diphenyl phosphorochloridate to give an N,N′-phosphorylated hydrazine derivative, designated as bis-(diphenoxyphosphinyl)hydrazine.

$$\underset{\text{I}}{(C_6H_5O)_2PON_2H_3} \begin{cases} \xrightarrow{\text{RCHO, } R_2CO} (C_6H_5O)_2PONHN{=}CHR({=}CR_2) \\ \xrightarrow{\text{ClCOOEt}} (C_6H_5O)_2PONHNHCOOEt \\ \xrightarrow{(C_6H_5O)_2POCl} [-NHPO(OC_6H_5)_2]_2 \end{cases}$$

The hydrazidate (I) is saponified (cleavage of the P—O bond) by warm aqueous sodium hydroxide, but the P—N bond appears to be unaffected under these conditions. Slow attack of the P—N bond takes place in aqueous solution;

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[3] Abstracted from doctoral dissertations submitted to the Graduate College of the University of Illinois by Ralph Gher, Jr. (1952) and William Channing Smith (1954).

[4] Compounds described in this paper have been subjected to pharmacological study at the Eli Lilly Laboratories, Indianapolis, Ind., and to general screening tests as agricultural chemicals by Dr. F. W. Slife of the Department of Agronomy of the University of Illinois, Urbana, Ill. Results will be published elsewhere.

solvolysis occurs in glacial acetic acid in the presence of hydrochloric acid to precipitate hydrazine dihydrochloride. There is some indication that I possesses slight basic character and will form a very unstable hydrochloride. However, reaction with picric acid in ethanolic solution induces solvolysis to form hydrazine picrate.

Phenyl phosphorodihydrazidate (II), $C_6H_5OPO(N_2H_3)_2$, can be prepared by the reaction of the dichloridate with an ether slurry of 95% hydrazine (4). Its identity as a hydrazide was confirmed by preparation of the dibenzylidene derivative.

Because of the readiness with which the P—N bond is cleaved in acid solution it is possible to titrate solutions of the phosphorohydrazidates with standard iodate. This procedure may prove to be of general applicability in the quantitative determination of the hydrazine nitrogen in such organic phosphorus compounds.

EXPERIMENTAL[5]

Diphenyl phosphorohydrazidate (I). A solution of 12 ml. of 85% hydrazine hydrate (0.203 mole) in 48 ml. of 95% ethanol was treated dropwise with 26 g. (0.103 mole) of diphenyl phosphorochloridate. The heavy oily layer which had separated during the course of the extremely vigorous reaction was brought back into solution by the addition of distilled water. The product crystallized as a fine white powder after the solution was cooled in an ice-bath. Recrystallization from dilute ethanol gave 23.3 g. (88.3%) of (I), melting at 116° [lit. m.p. 112° (3)].

Anal. Calc'd for $C_{12}H_{13}N_2O_3P$: C, 54.54; H, 4.96; N, 10.61.
Found: C, 54.64; H, 4.99; N, 10.76.

Quantitative solubilities of I in grams per 100 g. of solvent at 25° were determined: water, 0.153; diethyl ether, 0.355; ethanol, 4.96; ethanol (95%), 5.66; chloroform, 4.15; isopropyl alcohol, 2.59; benzene, 0.545; *n*-propanol, 4.18; dioxane, 10.87.

The hydrazidate dissolves slowly in cold 1 *N* NaOH, but more rapidly when warmed. The odor of phenol becomes distinctly noticeable. That the P—N is unaffected by such treatment is confirmed by the fact that neither benzalazine nor diphenyl N^2-benzylidenephosphorohydrazidate is formed when the resulting solution is treated with benzaldehyde.

The compound undergoes slow hydrolysis in aqueous solution as shown by the observation that the *p*H of a saturated solution drops slowly from about 6.3 to 4.3 over a 19 hour period. The product also undergoes solvolysis in acetic acid and in ethanol; a precipitate of hydrazine dihydrochloride forms in several minutes after treatment with concentrated hydrochloric acid.

Since the P—N linkage in I is readily cleaved in acid solution, experiments were undertaken to determine if the procedure employed for the quantitative estimation of hydrazine by direct titration with iodate (4) in strong hydrochloric acid might be applicable to phosphorohydrazidates. Samples of I were dissolved in 20-ml. portions of 3 *N* HCl without heating and the resulting solutions were diluted further with 20-ml. portions of 9 *N* HCl and 10 ml. of H_2O. To each solution, now approximately 4.8 *N* in HCl, there was added dropwise and with continuous stirring about half the theoretical amount of standard iodate solution. Then 15 ml. of CCl_4 was added and the titration was continued until the red-brown color of liberated iodine in the CCl_4 layer changed to a light yellow. The end point could be observed with accuracy if the last few mls. of iodate were added at a rate of one drop every five seconds. Typical results demonstrate that the iodate method possesses high accuracy:

Duplicate samples of I weighing 0.1693 g. and 0.1679 g., were found to require 26.07 and

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[5] Melting points are uncorrected.

TABLE I

ALDEHYDE AND KETONE DERIVATIVES OF DIPHENYL PHOSPHOROHYDRAZIDATE (DIPHENOXYPHOSPHINYLHYDRAZONES)

Carbonyl Compound	M.P., °C.	Empirical formula	Analyses					
			Carbon		Hydrogen		Nitrogen	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzaldehyde	114	$C_{19}H_{17}N_2O_3P$	64.77	64.82	4.86	5.03	7.95	8.16
p-Hydroxybenzaldehyde	162	$C_{19}H_{17}N_2O_4P$	61.95	62.26	4.65	4.8	7.61	7.71
p-Methoxybenzaldehyde	150	$C_{20}H_{19}N_2O_3P$	62.82	62.57	5.0	4.87	7.33	7.35
o-Hydroxybenzaldehyde	151	$C_{19}H_{17}N_2O_4P$	61.95	62.24	4.65	4.62	7.61	7.68
Acetone	142	$C_{15}H_{17}N_2O_3P$	59.21	59.32	5.63	5.67	9.21	9.18
Cyclohexanone	101	$C_{18}H_{21}N_2O_3P$	62.75	62.78	6.1	6.22	8.14	8.43
p-Chloroacetophenone	127	$C_{20}H_{18}ClN_2O_3P$	59.93	60.05	4.53	4.62	6.99	7.22
Acetylacetone[a]	151	$C_{29}H_{30}N_4O_6P_2$	58.78	58.6	5.10	5.21	9.46	9.44

[a] Analytical data are given for the unrecrystallized material, since attempted recrystallization from ethanol was found to bring about decomposition. Attention is called to the fact that 2 moles of I react with acetylacetone.

25.58 ml. of 0.02505 *M* KIO_3. Required for hydrazine nitrogen in $(C_6H_5O)_2PON_2H_3$: 10.61. Found: 10.81 and 10.69.

Diphenoxyphosphinylhydrazones. Carbonyl derivatives of I were prepared by reaction of the components in absolute ethanol. Melting points and analytical data are summarized in Table I. These substances could also be designated as diphenyl N^2-alkylidene (or arylidene)—phosphorohydrazidates.

Diphenyl N^2-carbethoxyphosphorohydrazidate. A solution containing 5.28 g. of I (0.020 mole) and 1.09 g. (0.010 mole) of ethyl chloroformate in 60 ml. of $CHCl_3$ was refluxed for two hours. A precipitate believed to be I•HCl[6] was removed by filtration; the solution was concentrated and cooled to yield, after recrystallization from CCl_4, 3.10 g. (92.3%) of the desired product, m.p. 121–122°. The N-carbethoxy derivative is soluble in ethanol, hot chloroform, and hot carbon tetrachloride; moderately soluble in cold methanol and cold chloroform; slightly soluble in cold carbon tetrachloride and insoluble in diethyl ether and in hot or cold water.

Anal. Calc'd for $C_{15}H_{17}N_2O_5P$: C, 53.58; H, 5.10; N, 8.33.
Found: C, 53.40; H, 5.12; N, 8.26.

Bis-(diphenoxyphosphinyl)hydrazine. This substance previously had been prepared from I by heating the latter above its melting point until no further elimination of hydrazine was observed (3). It was described as a crystalline substance, but no melting point was recorded. This reaction is in effect a desolvation (dehydrazination) reaction that can be represented by the equation

$$2\ (C_6H_5O)_2PON_2H_3 \rightarrow N_2H_4 + [-NHPO(OC_6H_5)_2]_2$$

The same substance may be obtained by the interaction of I with diphenylphosphoro-

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[6] The chloroform-insoluble material was found to melt initially at 187–189° and weighed 2.53 g., corresponding to an 85% yield of a presumed hydrochloride salt of I. Attempts to purify this solid by recrystallization from methanol resulted in progressive lowering of the melting point. Consistent analytical results could not be obtained.

chloridate in chloroform solution. A solution containing 12 g. (0.05 mole) of I and 13 g. of the chloridate (0.05 mole) was refluxed gently for one half hour. Some hydrazine dihydrochloride (2.5 g.) which had precipitated on cooling was removed by filtration. The mother liquor was concentrated to half its volume and allowed to stand for 12 hours, after which a considerable quantity of material had precipitated. Repeated recrystallization was required to give a product with a constant melting point, 142°.

Anal. Calc'd for $C_{24}H_{22}N_2O_6P_2$: C, 58.15; H, 4.4; N, 5.64.
Found: C, 58.11; H, 4.63; N, 5.64.

Phenyl phosphorodihydrazidate (II). To a suspension of 30 ml. of 95% hydrazine (0.89 mole) in 350 ml. of ether there was added slowly with constant agitation 39.8 g. (0.188 mole) of phenyl phosphorodichloridate. The reaction temperature was controlled by the refluxing ether. Stirring was continued for an additional hour, after which the ether layer was decanted from the solid reaction product and the latter was extracted with 200 ml. of warm ethanol. The initial crystalline fraction consisted largely of hydrazine hydrochloride. A more substantial second fraction was repeatedly recrystallized from absolute ethanol to give a small amount of the desired compound in the pure state, m.p. 103°.[7] The dihydrazidate (II) is very soluble in water and in ethanol, soluble in propanol-2 and in *n*-propanol, and slightly soluble in ether.

Anal. Calc'd for $C_6H_{11}N_4O_2P$: C, 35.65; H, 5.44; N, 27.73.
Found: C, 35.33; H, 5.39; N, 27.53.

Phenyl N^2,N^2*-dibenzylidene phosphorodihydrazidate.* The benzaldehyde derivative of (II) was prepared by direct reaction of the components in 95% ethanol. The pure product, m.p. 174°, was obtained after recrystallization from dilute ethanol.

Anal. Calc'd for $C_{20}H_{19}N_4O_2P$: C, 63.54; H, 5.03; N, 14.81.
Found: C, 63.56; H, 5.08; N, 15.06.

SUMMARY

Diphenyl phosphorohydrazidate has been prepared by hydrazinolysis of the chloridate and found to react (a) with carbonyl compounds to yield the corresponding diphenoxyphosphinylhydrazones, (b) with chlorocarbonic ester to give the N^2-carbethoxy derivative, and (c) with the chloridate to form bis-(diphenoxyphosphinyl)hydrazine. The P—N linkage in hydrazidate is cleaved in acid solution; the hydrazine content can be determined quantitatively by iodate titration. Phenyl phosphorodihydrazidate is obtained by hydrazinolysis of the dichloridate; the phenyl N^2, N^2-dibenzylidene derivative was prepared to confirm identity of this substance.

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(3) EPHRAIM AND SACKHEIM, *Ber.*, **44**, 3416 (1911).
(4) AUDRIETH AND PENNEMAN, *Anal. Chem.*, **20**, 1058 (1948).
(5) STRECKER AND HEUSER, *Ber.*, **57**, 1364 (1924).

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[7] Described as a wax-like product by Strecker and Heuser (Ref. 5). No melting point is recorded.