and was quite similar to the phosphonate product obtained in the chloroacetamide reactions.

Diethyl ethoxycarbonylmethylphosphonate[8a,c] (IIb) was prepared from ethyl chloroacetate according to the same procedure for Ia. The phosphonate was obtained in 76% yield; b.p. 103° (1.2 mm.), n_D^{25} 1.4299. The infrared spectrum was almost identical with the phosphonate (IVa) except for the different absorptions of the ester (5.78μ) and amide (6.13μ) groups.

Diethyl 1-ethoxy-2,2-dichlorovinyl phosphate[2b,4] (Ib) was prepared in 57% yield from ethyl trichloroacetate according to the procedure of Allen and Johnson[2b]; b.p. 106° (0.7 mm.); n_D^{25} 1.4495. About 35% of unreacted ester was recovered. The double bond absorbed at 6.0μ with an absorbancy of 0.43.

Diethyl carbamoylmethylphosphonate. This is a general preparation of carbamoylmethylphosphonates when solid amides are used as starting materials. A slurry of 19.1 g. (0.205 mole) of 2-chloroacetamide, 34 g. (0.205 mole) of triethyl phosphite, and 55 ml. of *o*-xylene was heated (132–143°) until the evolution of ethyl chloride was rapid. The rate of evolution of ethyl chloride was slower after about 1.25 hr., but the reaction mixture was kept at 143° for 2 hr. longer. The solvent was distilled *in vacuo* and the residue was recrystallized from petroleum ether and ethyl acetate mixture.

Acknowledgments. We are indebted to Dr. B. Katlafsky and Mr. O. Kinast for the infrared spectra, to Drs. C. F. Callis and D. P. Ames of our Inorganic Division for the NMR data and to Messrs. J. L. O'Sullivan and O. S. Kring for the analytical data.

ST. LOUIS 4, MO.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, INSTITUTE OF TECHNOLOGY POLITECHNIKA AND INSTITUTE OF ORGANIC SYNTHESIS POLISH ACADEMY OF SCIENCES]

Synthesis of 2-(Pyridyl)ethylphosphonic Acids and Esters[1]

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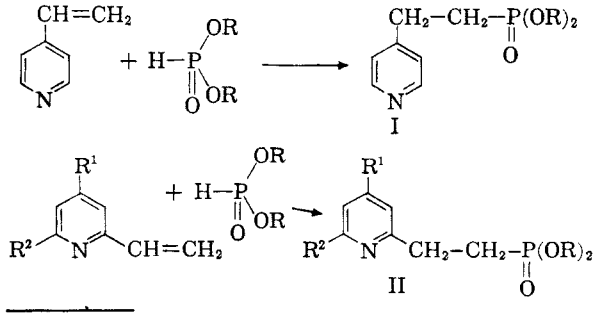
Esters of 2-(pyridyl)ethylphosphonic acids are obtained in good yield by adding dialkyl phosphites to α- and γ-vinylpyridines. The esters are readily hydrolyzed to the corresponding phosphonic acids.

Among phosphonic acids and their esters few compounds are known in which the phosphono or dialkylphosphono group is attached directly to the heterocyclic ring or its side chain.[2] In the field of pyridine the only compounds of this type are: 2-dimethylamino-5-pyridylphosphonic acid described by Plažek and Sasyk,[3] 3-pyridylphosphonic acid described recently by Bennett, Burger, and Volk,[4] pyridylhydroxymethylphosphonic acids reported by Burger, Clements, Dawson, and Henderson,[5] and 2-pyridylmethylphosphonic acids and their esters obtained in this laboratory.[6]

In undertaking the synthesis of still unknown esters of 2-(pyridyl)ethylphosphonic acids (I and II) it might have been expected that the preparation of this kind of compound by the Arbuzov or Michaelis-Nylen methods would entail difficulties due to the properties of the starting β-haloalkylpyridines. The latter, endowed with a tautomerically electron-withdrawing group, would likely be susceptible to dehydrohalogenation by attack of basic reagents, such as sodium dialkyl phosphites or trialkyl phosphites. This type of difficulty was noted by Arbuzov and Lugowkin in the course of the attempted synthesis of diethyl 2-(2′-pyridyl)-ethylphosphonate by the Michaelis-Nylen procedure.[7]

In considering other methods possibly useful in synthesizing compounds I and II we focused our attention on pyridine derivatives possessing vinyl groups in position α or γ. Such vinylpyridines behave like typical α,β-unsaturated compounds and add nucleophilic reagents.[8] In view of these facts we expected to synthesize esters I and II by adding dialkyl phosphites, as nucleophilic reagents, to α and γ-vinylpyridines. We found indeed that dialkyl phosphites add to 2 and 4-vinylpyridines as well as to 2-methyl-6-vinylpyridine and 2,4-



(1) Preliminary communication: *Bull. acad. polon. sci., Classe III*, 6, 19 (1958).

(2) L. D. Freedman and G. O. Doak, *Chem. Revs.*, **57**, 479 (1957).

(3) E. Plažek and Z. Sasyk, *Roczniki Chem.*, **14**, 1198 (1934); *Chem. Zentr.*, **1935**, I, 2177.

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(5) A. Burger, J. B. Clements, N. D. Dawson, and R. B. Henderson, *J. Org. Chem.*, **20**, 1383 (1955).

(6) E. Maruszewska-Wieczorkowska, J. Michalski, and A. Skowrońska, *Roczniki Chem.*, **30**, 1197 (1956).

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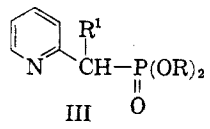
(8) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

dimethyl-6-vinylpyridine in accordance with the illustrated scheme. The addition reaction scheme assumed is supported by the following facts. The picrolonate of the addition product II(R = C_2H_5, R^1 = R^2 = H) differed considerably from that of the compound III (R = C_2H_5, R^1 = CH_3) which results from the alternative direction of addition. This compound was obtained by alkylation of the potassium diethyl 2-pyridylmethylphosphonate III (R = C_2H_5, R^1 = H).[6] The



III

benzylamine salts of the corresponding acids also were different.

Addition reactions were run without solvent and with sodium ethoxide as catalyst. Under the experimental conditions addition of dialkyl phosphites to 4-vinylpyridine takes place even at room temperature and is distinctly exothermic, but reaction with 2-vinylpyridines requires brief heating. Addition takes place also without a basic catalyst, but then requires prolonged heating in boiling xylene. Here the pyridine bases themselves probably act as catalysts. In reaction run without a catalyst, the yields of addition products are lower and considerable amounts of polymeric substances are formed. The molar ratio in which the reagents are used has no appreciable effect on the yield. Esters I and II are high boiling oils, soluble in water, showing the character of weak tertiary bases. They are readily converted into picrolonates and chloroplatinates. Acid hydrolysis of the esters leads to the corresponding phosphonic acids I (R = H) and II (R = H), which unlike the homologous 2-pyridylmethylphosphonic acid III (R = R^1 = H) are capable of forming hydrochlorides.[6] The physical constants of esters I and II and of the corresponding acids are given in the Table I.

EXPERIMENTAL

Typical examples of experimental procedure are given below, and the rest are summarized in Table I. All melting and boiling points are uncorrected. The picrates and picrolonates were prepared by standard procedures.

Diethyl 2-(2'-pyridyl)ethylphosphonate. (*a*) A solution of 2-vinylpyridine (12.6 g., 0.12 mole) and of diethyl phosphite (13.8 g., 0.1 mole) in 60 ml. of xylene was gently refluxed under an atmosphere of carbon dioxide for 18 hr. The solvent and unchanged reactants were removed under reduced pressure. The oily residue was distilled *in vacuo* to give 9.7 g. (40%) of 2-(2'-pyridyl)ethylphosphonate, b.p. 101° at 0.05 mm., n_D^{25} 1.4938, n_D^{30} 1.4920, d_4^{25} 1.1156.

(*b*) A solution of sodium ethoxide in ethanol (0.7 g. of sodium in 20 ml. of ethanol) was added dropwise with stirring to a mixture of 2-vinylpyridine (21 g., 0.2 mole) and diethyl phosphite (27.6 g., 0.2 mole). After the addition was completed the mixture was stirred at 60–70° for 3 hr. After standing overnight at room temperature 200 ml. of chloroform was added. The solution formed, after washing with water (2 × 10 ml.), was dried over magnesium sulfate. The solvent was evaporated *in vacuo*, and the oily residue distilled under reduced pressure, to give 29.2 g. (60%) of diethyl 2-(2'-pyridyl)ethylphosphonate, b.p. 112–113° at 0.2 mm., n_D^{25} 1.4936.

Diisopropyl 2-(2'-pyridyl)ethylphosphonate. A solution of diisopropyl phosphite (33.2 g., 0.2 mole) and 2-vinylpyridine (26 g., 0.25 mole) in 45 ml. of toluene was refluxed for 9 hr. and separated substantially as described in previous experiments. to give 10.8 g. (20%) of the desired product, b.p. 99° at 0.05 mm., n_D^{25} 1.4812, n_D^{30} 1.4792, d_4^{25} 1.0691.

2-(2'-Pyridyl)ethylphosphonic acid hydrochloride. A solution containing diethyl 2-(2'-pyridyl)ethylphosphonate (6.1 g., 0.025 mole) in 50 ml. of 20% hydrochloric acid was refluxed for 5 hr. and evaporated to dryness on a steam bath under reduced pressure. After recrystallization from absolute ethanol the white hygroscopic needles melted at 165–166°. Yield 4.2 g. (75%).

2-(2'-Pyridyl)ethylphosphonic acid. To a solution containing 2-(2'-pyridyl)ethylphosphonic acid hydrochloride (1.0 g.) in 5 ml. of water, sodium bicarbonate (0.37 g.) was added. The solution formed was evaporated to dryness *in vacuo*. The solid residue was extracted twice with hot ethanol. The combined hot solution was filtered off and allowed to cool slowly to room temperature. Almost pure colorless needles of 2-(2'-pyridyl)ethylphosphonic acid were collected (0.6 g., 71%), m.p. 149–150°.

When 2-(2'-pyridyl)ethylphosphonic acid was crystallized from dilute ethanol, the dihydrate was obtained as large white needles, m.p. 53–54°. If the dihydrate was heated at 100° a white crystalline solid formed. After recrystallization from ethanol this melted at 149–150° and gave no melting point depression with a laboratory sample of 2-(2'-pyridyl)-ethylphosphonic acid.

Anal. Calcd. for $C_7H_{10}NO_3P \cdot 2H_2O$: 16.1% H_2O. Found: 16.0% H_2O.

Benzylammonium salt of 2-(2'-pyridyl)ethylphosphonic acid. To a solution of 2-(2'-pyridyl)ethylphosphonic acid (0.15 g.) in 10 ml. of absolute ethanol, benzylamine (0.2 g.) in 25 ml. of acetone was added. The crystalline benzylamine salt was collected, washed with acetone, and dried under vacuum (0.21 g.). Recrystallization from a mixture of ethanol and acetone yielded white light needles, m.p. 178–179°, very soluble in water and ethanol.

Diethyl 1-(2'-pyridyl)ethylphosphonate. In a three-necked flask, equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser provided with a calcium chloride tube, potassium (3.9 g., 0.1 mole) in 100 ml. of benzene was placed. Diethyl 2-pyridylmethylphosphonate (22.9 g., 0.1 mole) was added dropwise with vigorous agitation. After the potassium was dissolved, methyl iodide (14.2 g., 0.1 mole) was added dropwise, and when the vigorous reaction had subsided, the mixture was heated at 50° for 3 hr. The flask was cooled to room temperature, and the mixture filtered off. Potassium iodide which separated was washed with benzene (100 ml.). The combined benzene solutions were washed with water (30 ml.) and dried over magnesium sulfate. After removing the solvent *in vacuo*, the residue was distilled under reduced pressure to give 12.2 g. (50%) of diethyl 1-(2'-pyridyl)ethylphosphonate, b.p. 91–92° at 0.2 mm., n_D^{25} 1.4922, n_D^{30} 1.4902, d_4^{25} 1.1092.

Anal. Calcd. for $C_{11}H_{18}NO_3P$: P, 12.8; N, 5.8. Found: P, 12.3; N, 5.6.

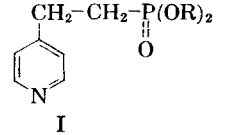
The picrolonate crystallized from benzene in yellow plates, m.p. 141–143° (dec.). It showed considerable melting point depression in admixture with the isomeric picrolonate of diethyl 2-(2'-pyridyl)ethylphosphonate, prepared by addition of diethyl phosphite to 2-vinylpyridine.

Anal. Calcd. for $C_{21}H_{26}N_8O_8P$: P, 6.1; N, 13.8. Found: P, 6.3; N, 13.8.

Di(benzylammonium)salt of 1-(2'-pyridyl)ethylphosphonic acid. A solution containing diethyl 1-(2'-pyridyl)ethylphos-

TABLE I

PROPERTIES OF 2-(PYRIDYL)ETHYLPHOSPHONIC ACIDS AND DERIVATIVES



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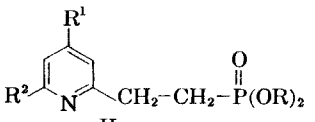

II

Compound	Yield,[a] %	M.P., °C. (B.P., °/Mm.)	n_D^{25}	d_4^{25}	Formula	Analyses, % Calcd. P	Calcd. N	Found P	Found N	Comments[b]
II; R = R¹ = R² = H		149–150			$C_7H_{10}NO_3P$	16.6	7.5	16.5	7.3	White needles, E
										Dihydrate m.p. 53–54°
Hydrochloride		165–166			$C_7H_{11}ClNO_3P$	13.9	6.3	13.9	6.6	White hygroscopic needles, E
Benzylammonium salt		178–179			$C_{14}H_{19}H_2O_3P$	10.5	9.5	10.6	9.5	White needles, E + A
II; R = C_2H_5; R¹ = R² = H	40 (60)	(101/0.05)	1.4938	1.1156	$C_{11}H_{18}NO_3P$	12.8	5.8	12.4	6.1	
Picrolonate		91–92			$C_{21}H_{26}N_5O_8P$	6.1	13.8	6.1	13.8	Yellow needles, B
II; R = *n*-C_3H_7; R¹ = R² = H	51	(105/0.01)	1.4880	1.0725	$C_{13}H_{22}NO_3P$	11.4	5.2	11.1	5.6	
Picrolonate		98–99			$C_{23}H_{30}N_5O_8P$		13.1		13.0	Yellow needles, B + L
II; R = iso-C_3H_7; R¹ = R² = H	20	(99/0.05)	1.4812	1.0681	$C_{13}H_{22}NO_3P$	11.4	5.2	11.1	5.2	
Picrolonate		134–135 dec.			$C_{23}H_{39}N_5O_8P$		13.1		13.1	Yellow needles, B + L
II; R = *n*-C_4H_9; R¹ = R² = H	43 (65)	(132/0.2)	1.4841	1.0460	$C_{15}H_{26}NO_3P$	10.3	4.7	10.3	4.8	
II; R = iso-C_4H_9; R¹ = R² = H	38	(117/0.1)	1.4820	1.0381	$C_{15}H_{26}NO_3P$	10.3	4.7	9.9	4.8	
Picrolonate		100			$C_{25}H_{34}N_5O_8P$		12.5		12.8	Yellow platelets, T
II; R = R¹ = H; R² = CH_3		169–171			$C_8H_{12}NO_3P$[c]		7.0		6.9	White, hygroscopic microcrystalline powder, E + T
II; R = C_2H_5; R¹ = H; R² = CH_3	(56)	(102/0.05)	1.4899	1.0858	$C_{12}H_{20}NO_3P$	12.1	5.4	11.9	5.6	
Picrolonate		148–149			$C_{22}H_{28}N_5O_8P$	6.0		6.1		Yellow needles, T + C
II; R = H; R¹ = R² = CH_3		213–214			$C_9H_{14}NO_3P$[d]		6.5		6.2	White small plates, E + T
II; R = C_2H_5; R¹ = R² = CH_3	(61)	(109/0.1)	1.4919	1.0746	$C_{13}H_{22}NO_3P$[e]	11.4		11.2		
I; R=H		225–227 dec.			$C_7H_{10}NO_3P$	16.6	7.5	16.2	7.6	White small plates, E + W
Hydrochloride		139–141			$C_7H_{11}ClNO_3P$	13.9	6.3	14.0	6.4	White small hygroscopic plates, E
I; R = C_2H_5	(81)	(117/0.2)	1.4935	1.1267	$C_{11}H_{18}NO_3P$	12.8	5.8	12.7	5.8	
Picrate		132–133			$C_{17}H_{21}N_4O_{10}P$	6.6	11.8	6.8	11.5	Yellow plates, E

[a] The yields quoted in parentheses refer to reactions conducted in the presence of sodium ethoxide. [b] Solvents for recrystallization: W, water; E, ethanol; A, acetone; B, benzene; L, ligroin; T, carbon tetrachloride; C, chloroform. [c] Calcd.: C, 47.8; H, 6.0. Found: C, 47.2; H, 6.0. [d] Calcd.: C, 50.2; H, 6.5. Found: C, 50.5; H, 6.9. [e] Calcd.: C, 57.6; H, 8.1. Found: C, 57.3; H, 8.3.

phonate (1 g.) in 10 ml. 20% hydrochloric acid was refluxed for 5 hr. and evaporated to dryness under reduced pressure. The oily residue was dissolved in ethanol and an excess benzylamine (1.3 g.) was added. The precipitated di(benzylammonium)salt was separated by filtration and washed with ethanol (1.5 g.). Recrystallization from ethanol yielded white needles, m.p. 171°.

Anal. Calcd. for $C_{21}H_{28}N_3O_3P$: P, 7.7; N, 10.5. Found: P, 7.6; N, 10.4.

2-[6'-(2'-Methylpyridyl)]ethylphosphonic acid. A solution containing diethyl 2-[6'-(2'-methylpyridyl)]ethylphosphonate (2 g.) in 20 ml. 20% hydrochloric acid was refluxed for 5 hr. The solution obtained was evaporated under reduced pressure. The residue was dissolved in small amount of water and evaporated *in vacuo*. This operation was repeated twice. Crude hydrochloride (1.8 g.) was dissolved in water (10 ml.) and sodium bicarbonate (0.7 g.) was added. The solution was evaporated to dryness *in vacuo* and the acid extracted with hot absolute ethanol. The alcohol solution was concentrated to small volume. The solid acid was collected (1.1 g.) and recrystallized from ethanol. White, very hygroscopic small plates, m.p. 169–171°, appeared.

Diethyl 2-(4'-pyridyl)ethylphosphonate. A solution of sodium ethoxide in ethanol was added dropwise with stirring to a mixture of 4-vinylpyridine (21 g., 0.2 mole) and of diethyl phosphite (27.6 g., 0.2 mole). After 15 min. the temperature rose to 70°, and was kept at 50° by occasional cooling. The product was isolated in the usual manner, b.p. 117° at 0.2 mm., n_D^{25} 1.4935, n_D^{30} 1.4916, d_4^{25} 1.1267. Yield 39.3 g., 81%.

LODZ, POLAND

[CONTRIBUTION FROM THE WILLIAM ALBERT NOYES LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Nitrogen Compounds of the Phosphoric and Phosphonic Acids. IV. Some Derivatives of Phenylphosphonamidic and Phenylphosphonamidothioic Acids

M. F. HERSMAN[1,2] AND L. F. AUDRIETH

Received July 11, 1958

Partial solvolysis of phenylphosphonic dichloride with an alcohol (or a phenol) in the presence of pyridine in ether or benzene leads to formation of the *O*-alkyl (aryl) phosphonochloridates. These intermediates can be converted by ammonolysis into the *O*-alkyl-*P*-phenylphosphonamidates, $C_6H_5PO(OR)(NH_2)$, where R = Me, Et, *n*-Pr, *n*-Bu, *n*-Am, Ph, and by aminolysis into the *O*-alkyl (aryl)-*P*-phenylphosphonamidates, $C_6H_5PO(OR)(NX_2)$, where R = C_6H_5 and NX_2 = $-NHC_6H_5$, $-N(CH_2)_4CH_2$, $-NC_2H_4OCH_2CH_2$, $-NHCH_2CH(CH_3)_2$, and R = C_2H_5 and NX_2 = $-NHC_6H_5$. Some typical *O*-alkyl (aryl)-*N*-alkyl (aryl)-*P*-phenylphosphonamidothioates, $C_6H_5PS(OR)(NX)_2$, were also prepared by partial solvolysis followed by aminolysis of the intermediate *P*-phenylphosphonochloridothioate, $C_6H_5PS(OR)Cl$. The *O*-alkyl phosphonochloridates undergo thermal decomposition to yield the corresponding alkyl chlorides and the *P*-phenyl metaphosphonate, $(C_6H_5PO_2)_X$.

A significant feature of compounds having a phosphorus-halogen linkage is their ability to undergo solvolytic reactions with compounds possessing a labile hydrogen atom. In alkyl (and aryl) phosphonic dichlorides, ($RPOCl_2$), the presence of a phosphorus to oxygen bond imparts to the phosphorus-chlorine bond properties similar to those of the acid chlorides of the carbon family. Due to the electronegative character of the groups attached to the phosphorus atom, the latter becomes electron deficient and therefore prone to nucleophilic attack. The chlorine atoms of alkyl (and aryl) phosphonic dichlorides can, however, be made to react in a stepwise fashion. The second chlorine atom is much less reactive than the first. Partial solvolysis of the alkyl (aryl) phosphonic dichloride leads to formation of an intermediate ester-chloridate when reaction with an alcohol is allowed to take place. The oxygen atom thus introduced as an alkoxy group into the molecule is electron rich and has a tendency to donate electrons instead of withdrawing them as is the case with chlorine atoms; it thereby serves to reduce the partial positive charge on the phosphorus atom and, in turn, to reduce the reactivity of the remaining halogen atom.

These considerations, however, are not meant to imply that the second chlorine atom will not undergo reaction under appropriate circumstances, but only that the replacement reaction takes place less vigorously. In the usual cases, most solvolytic reactions of alkyl (aryl) phosphonic dichlorides involve replacement of both chlorine atoms since an excess of the solvolytic agent is generally employed. Examples of stepwise reaction are relatively few.

The investigations described in the present publication are concerned with the preparation and characterization of some phenyl phosphonic and phosphonothioic acid derivatives containing both P—O (or P—S) and P—N linkages, such as $C_6H_5PO(OR)(NX_2)$, where R = alkyl and aryl, and NX_2 = amide and primary, or secondary amine radicals. This study was undertaken initially to develop a new route to the preparation of the alkyl-

(1) Abstracted from the doctoral dissertation submitted to the Graduate College of the University of Illinois by M. F. Hersman (1958).

(2) Victor Chemical Works Research Fellow at the University of Illinois, 1955–56. The authors desire to express their appreciation for the assistance rendered by Dr. A. D. F. Toy, of the Victor Chemical Works Research Laboratory, during the course of the present investigation.