The Preparation of Organic Phosphorus Compounds by Ivanov Reactions. I[1,2]

F. F. BLICKE AND S. RAINES

College of Pharmacy, University of Michigan, Ann Arbor, Michigan

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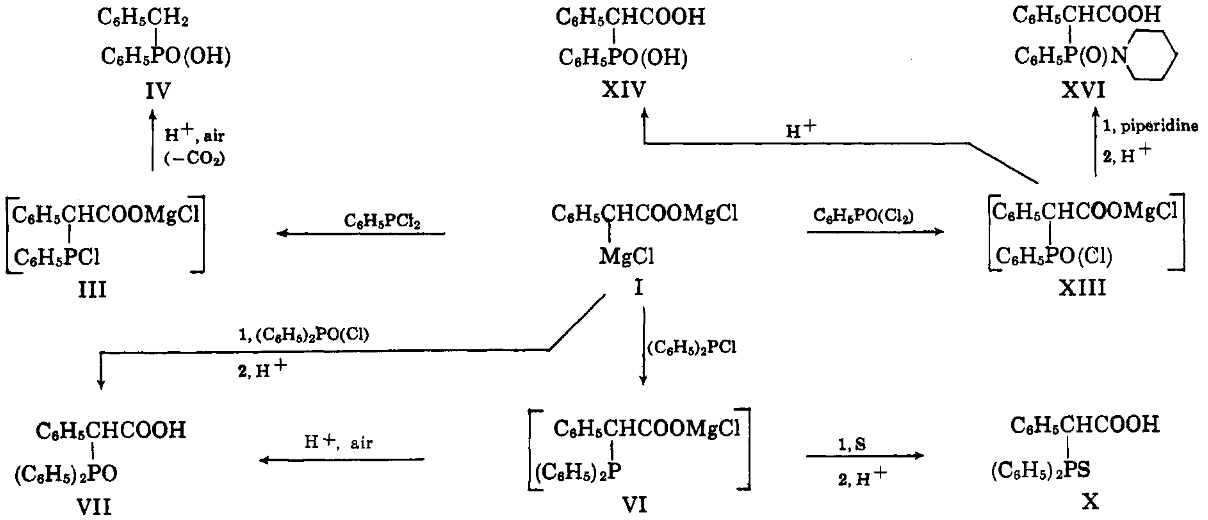
Organic phosphorus compounds have been obtained by reaction of $C_6H_5CH(MgCl)COOMgCl$ and $C_6H_5CH(MgCl)CON(CH_3)_2$ with phenyldichlorophosphine, diphenylchlorophosphine, phenyldichlorophosphine oxide, and diphenylchlorophosphine oxide.

In studies of the scope of the Ivanov reaction with respect to the preparation of organic compounds of phosphorus, reactions were carried out with the use of the Ivanov reagent $C_6H_5CH(MgCl)COOMgCl$ (I) and the Ivanov-like reagent $C_6H_5CH(MgCl)CON(CH_3)_2$ (II). These reagents were prepared by reaction of isopropylmagnesium chloride with phenylacetic acid and with N,N-dimethylphenylacetamide, respectively.

Reagent I reacted with phenyldichlorophosphine to form the unisolated intermediate III which, after treatment with dilute acid, underwent hydrolysis, air oxidation, and decarboxylation to yield phenylbenzylphosphinic acid (IV). The structure of this acid was established by its synthesis from phenyldichlorophosphine oxide and benzylmagnesium chloride in the presence of pyridine.[3] Diazomethane converted IV into methyl phenylbenzylphosphinate (V).



After reaction of I with diphenylchlorophosphine the reaction mixture, which contained VI, was acidified. Air oxidation took place and phenyl(diphenylphosphinyl)acetic acid (VII) was isolated. This acid was obtained also by interaction of I with diphenylchlorophosphine oxide. When heated above its melting point, VII underwent decarboxylation to form diphenylbenzylphosphine oxide (VIII). Diazomethane converted VII into methyl phenyl(diphenylphosphinyl)-acetate (IX). Other procedures have been used to prepare VII[4] and VIII.[5-8]

After VI, in the reaction mixture, had been treated with sulfur and the mixture had been acidified, phenyl(diphenylphosphinothioyl)acetic acid (X) was isolated and converted into methyl phenyl(diphenylphosphinothioyl)acetate (XI) by diazomethane. After reaction of the nonisolated VI with methyl iodide and acidification of the reaction mixture, decarboxylation took place and diphenylbenzylmethylphosphonium iodide (XII) was obtained; this product has been synthesized by other procedures.[8,9]

Reagent I and phenyldichlorophosphine oxide reacted to form XIII which, after acidification of the reaction mixture, was converted into phenyl(phenylhydroxyphosphinyl)acetic acid (XIV); diazomethane transformed the acid into methyl phenyl(phenylmethoxyphosphinyl)acetate (XV). The presence of chlorine in the nonisolated, initial reaction product XIII was shown by the addition of piperidine to the reaction mixture; after acidification, phenyl(phenylcarboxymethyl)(N,N-pentamethylene)phosphinic amide (XVI) was produced. Diazomethane converted XVI into phenyl(phenylcarbomethoxymethyl)(N,N-pentamethylene)phosphinic amide (XVII).

After reaction of reagent II with diphenylchlorophosphine to form XVIII and then acidification of the reaction mixture, the product was converted by air oxidation into N,N-dimethylphenyl(diphenylphosphinyl)acetamide (XIX). This product was heated with aqueous potassium hydroxide and the reaction mixture, which contained XX, was then acidified whereupon decarboxylation took place and diphenylbenzylphosphine oxide (VIII) was produced. When

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[2] This investigation was supported by grants from The Wm. S. Merrell Co. and from the American Foundation for Pharmaceutical Education.

[3] See G. M. Kosolapoff, *J. Am. Chem. Soc.*, **72**, 5508 (1950).

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[6] A. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **42**, 395 (1910); *Chem. Abstr.*, **5**, 1397 (1911).

[7] A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948); *Chem. Abstr.*, **43**, 3801 (1949).

[8] H. Hoffmann, R. Grünewald, and L. Horner, *Ber.*, **93**, 861 (1960).

[9] L. Horner, P. Beck, and H. Hoffmann, *ibid.*, **92**, 2093 (1959).

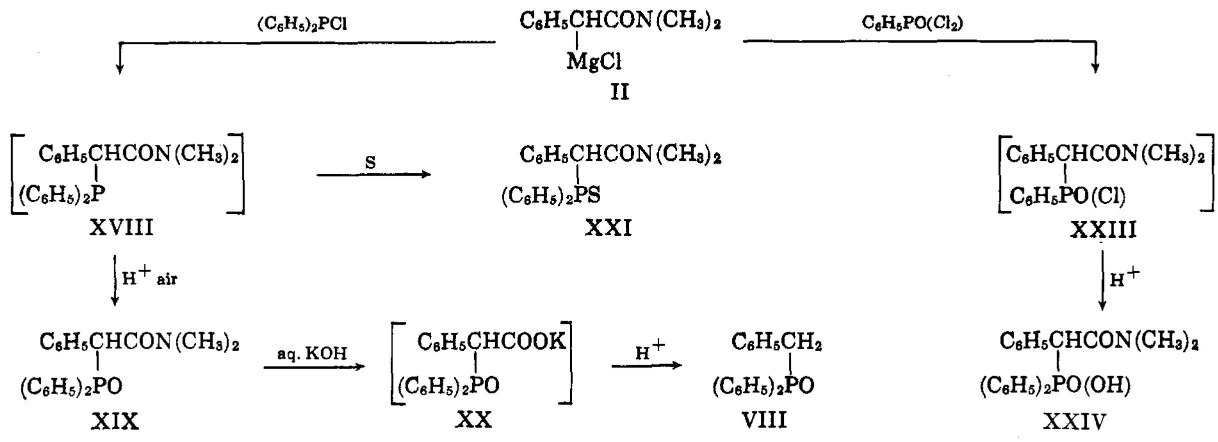

TABLE I

PRODUCTS OBTAINED FROM $C_6H_5CH(MgCl)COOMgCl$

	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %		Phosphorus, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
IV	178–180	30	$C_{13}H_{13}O_2P^a$	67.24	67.53	5.64	5.79	13.34	13.24
V	89–92	59	$C_{14}H_{15}O_2P$	68.29	68.31	6.14	6.33	13.00	12.89
VII	135–137[b]	16[c], 81[d]	$C_{20}H_{17}O_3P$						
IX	205–207	91	$C_{21}H_{19}O_3P$	71.99	72.18	5.47	5.67	8.84	9.10
X	203–205	43	$C_{20}H_{17}O_2PS^e$	68.16	68.30	4.86	5.02	8.79	8.84
XI	118–120	70	$C_{21}H_{19}O_2PS^f$	68.84	68.69	5.23	5.27	8.45	8.56
XII	235–237[g]	61	$C_{20}H_{20}PI$	57.43	57.63	4.82	5.02		
XIV	79–81	58	$C_{14}H_{13}O_4P$	60.87	61.12	4.74	4.92	11.21	11.10
XV	86–88	16	$C_{16}H_{17}O_4P$	63.15	63.22	5.63	5.56		
XVII[h]	149–151	12	$C_{20}H_{24}O_3NP$	67.20	67.54	6.77	7.02	8.67	8.50

[a] Calcd. neut. equiv., 232.2. Found, 232.5. [b] Ref. 4, m.p. 136°. [c] Obtained from $(C_6H_5)_2PCl$. [d] Obtained from $(C_6H_5)_2PO(Cl)$. [e] *Anal.* Calcd.: S, 9.11. Found: S, 9.28. [f] *Anal.* Calcd.: S, 8.75. Found: S, 8.81. [g] Ref. 8, m.p. 229–230°. [h] Compounds IV and XII were recrystallized from absolute ethanol; V from petroleum ether (b.p. 90–100°); VII from nitromethane; X from acetic acid; IX from 2-butanone; XI from absolute ethanol after the oil had been triturated with ether; XV, a semisolid, was placed on a porous plate and the solid material was recrystallized from petroleum ether (b.p. 90–100°); XVII, a semisolid, was dissolved in hot petroleum ether (b.p. 90–100°) and the gum which separated from the cold solution was washed with acetone.

TABLE II

PRODUCTS OBTAINED FROM $C_6H_5CH(MgCl)CON(CH_3)_2$

	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %		Phosphorus, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
XIX	270–272	41	$C_{22}H_{22}O_2NP$	72.71	72.42	6.10	6.11	8.52	8.75
XXI	189–191	48	$C_{22}H_{22}ONPS^a$	69.63	69.68	5.83	5.78	8.16	8.16
XXII	237–239	54	$C_{23}H_{25}ONPI^b$	56.45	56.51	5.15	5.19	6.30	6.17
XXIV	202–204	28	$C_{16}H_{18}O_3NP$	63.36	63.43	5.98	6.06	10.21	10.14
XXV[c]	180–182	63	$C_{17}H_{20}O_3NP$	64.34	64.35	6.35	6.31	9.76	9.65

[a] *Anal.* Calcd.: S, 8.45. Found: S, 8.52. [b] *Anal.* Calcd.: I, 25.93. Found: I, 26.03. [c] Compounds XIX and XXI were recrystallized from nitromethane, XXII from ethanol, XXIV from dioxane, and XXV from 2-butanone.

the original reaction mixture, which contained XVIII, was treated with sulfur the product formed was N,N-dimethylphenyl(diphenylphosphinothioyl)acetamide (XXI). Reaction of XVIII with methyl iodide yielded the methiodide (XXII). The initial, nonisolated reaction product XXIII produced by reaction of II with phenyldichlorophosphine oxide was converted into N,N-dimethylphenyl(phenylhydroxyphosphinyl)acetamide (XXIV) when the reaction mixture was acidified. Diazomethane converted XXIV into N,N-dimethylphenyl(phenylmethoxyphosphinyl)acetamide (XXV).

Experimental

Products obtained from reagents I and II are listed in Tables I and II, respectively.

After a reaction had been carried out, the reaction mixture was hydrolyzed in one of the following ways: (a) the reaction mixture was poured into a mixture of 15 ml. of concentrated hydrochloric acid, 200 ml. of water and ice; (b) a mixture of 18 ml. of concentrated hydrochloric acid and 180 ml. of water was added, dropwise and very slowly, to the stirred reaction mixture which was cooled in an ice bath; (c) 6 g. of ammonium chloride, dissolved in 220 ml. of water, was added, dropwise, to the stirred reaction mixture.

Preparation of $C_6H_5CH(MgCl)COOMgCl$ (I).—Phenylacetic acid (13.6 g., 0.1 mole), dissolved in 100 ml. of sodium-dried benzene, was added, dropwise, to a stirred solution of isopropylmagnesium chloride which had been prepared from 18.0 g. (0.22 mole) of isopropyl chloride, 5.4 g. (0.22 g.-atom) of magnesium, 1 ml. of ethyl bromide, and 150 ml. of ether. The mixture was stirred for 12 hr.

Phenylbenzylphosphinic Acid (IV). A.—The suspension of reagent I was transferred to a dropping funnel and added, dropwise, to a stirred solution of 17.9 g. (0.1 mole) of phenyldichlorophosphine in 25 ml. of benzene. The mixture was stirred for 12 hr., hydrolyzed by method a and the organic layer was extracted with aqueous sodium bicarbonate. After acidification of the alkaline layer, the mixture was extracted with benzene, and the solvent was removed from the dried extract. The oily residue was dissolved in hot chloroform. After some time, the precipitated solid was filtered and triturated with hot petroleum ether (b.p. 60–70°) to remove phenylacetic acid.

B.—Pyridine (7.9 g., 0.1 mole) was added, dropwise, to a stirred mixture of 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide and 200 ml. of ether, and the material was stirred for 4 hr. A solution of benzylmagnesium chloride, which had been prepared from 12.7 g. (0.1 mole) of benzyl chloride, 2.4 g. (0.1 g.-atom) of magnesium, and 100 ml. of ether, was added, dropwise, to the stirred material. After the reaction mixture had been stirred for 4 hr., a mixture of 20 ml. of concentrated hydrochloric acid and 200 ml. of water was added. The organic layer was shaken with aqueous sodium bicarbonate and the alkaline layer was acidified with hydrochloric acid. The precipitated product was recrystallized from absolute ethanol; yield, 5.3 g. (23%); m.p. and m.m.p. 178–180°.

Esters V, IX, XI, XV, XVII, and XXV.—The required acid was dissolved or partially dissolved in a suitable solvent. Methanol was used for the preparation of IX and XXV, and dioxane for the synthesis of the other esters. After the addition of excess diazomethane, dissolved in ether, the solvents were removed and the residue, with two exceptions, was dissolved in benzene; the residues of crude XVII and XXV were dissolved in chloroform. The solution was extracted with aqueous sodium bicarbonate and the solvent was removed from the dried organic layer.

Phenyl(diphenylphosphinyl)acetic Acid (VII). A.—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to I, the mixture was stirred for 12 hr. and then hydrolyzed by method b. The organic layer was extracted with aqueous sodium bicarbonate, the alkaline solution was acidified, extracted with chloroform, and the solvent was removed from the dried organic layer. The residue was recrystallized from nitromethane. During this process decarboxylation took place to a slight extent. The recrystallized material was treated with aqueous sodium bicarbonate, the mixture was filtered, and the filtrate acidified, whereupon VII precipitated.

B.—Diphenylchlorophosphine oxide (23.7 g., 0.1 mole) was added, dropwise, to the stirred suspension of I. The mixture was refluxed for 3 hr., stirred for 12 hr., and hydrolyzed by method b. The precipitate, which formed between the organic and aqueous layer, was removed by filtration and recrystallized from nitromethane. This material was treated with aqueous sodium bicarbonate and, after filtration, the filtrate was acidified; the product precipitated.

Phenyl(diphenylphosphinothioyl)acetic Acid (X).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of I and the mixture was stirred for 12 hr. A solution of 6.4 g. (0.2 g.-atom) of sulfur in 75 ml. of carbon disulfide was added dropwise. The mixture was refluxed for 1 hr., stirred for 12 hr. and hydrolyzed by method b. The organic layer was separated and shaken with aqueous sodium bicarbonate. The insoluble material which formed between the organic and alkaline layer was removed by filtration and triturated with dilute hydrochloric acid. After the addition of benzene, which dissolved the material, the organic layer was separated, dried, and the solvent was removed.

Diphenylbenzylmethylphosphonium Iodide (XII).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of I. After the mixture had been stirred for 12 hr., 21.3 g. (0.15 mole) of methyl iodide was added dropwise; the material was stirred for 12 hr. and hydrolyzed by method a. The solid material which formed between the organic and aqueous layer was removed by filtration and recrystallized.

Phenyl(phenylhydroxyphosphinyl)acetic Acid (XIV).—After 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide had been added to I, the mixture was refluxed for 1 hr. and then hydrolyzed by method b. The organic layer was extracted with aqueous sodium bicarbonate; the alkaline layer was acidified and extracted with chloroform. The solvent was removed from the dried extract. The oily residue became solid and pure after it had been triturated with petroleum ether (b.p. 30–40°) and then with hot petroleum ether (b.p. 60–70°).

Phenyl(phenylcarboxymethyl)(N,N-pentamethylene)phosphinic Amide (XVI).—After the addition of 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide to a stirred suspension of I, the mixture was stirred for 6 hr. Piperidine (17.0 g., 0.2 mole) was added, dropwise, to the mixture which was then stirred for 12 hr. and hydrolyzed by method b. The organic layer was extracted with aqueous bicarbonate; the alkaline layer was acidified and extracted with benzene. After removal of the solvent from the dried benzene layer, the oily residue was triturated with hot petroleum ether (b.p. 90–100°). The solid product was dissolved in hot carbon tetrachloride, and petroleum ether (b.p. 90–100°) was added until the product precipitated. The impure material (20.8 g., 61%) melted at 130–150°. After the carbon tetrachloride–petroleum ether process had been repeated a number of times, 8.8 g. of product was obtained which melted at 145–148°. An analysis showed that this material was still impure.

Preparation of $C_6H_5CH(MgCl)CON(CH_3)_2$ (II).—N,N-Dimethylphenylacetamide (16.3 g., 0.1 mole), dissolved in 150 ml. of sodium-dried benzene, was added, dropwise, to a stirred solution of isopropylmagnesium chloride which had been prepared from 2.7 g. (0.11 g.-atom) of magnesium, 8.7 g. (0.11 mole) of isopropyl chloride, 1 ml. of ethyl bromide, and 200 ml. of ether. The mixture was stirred and refluxed for 1 hr. and then stirred for 12 hr.

N,N-Dimethylphenyl(diphenylphosphinyl)acetamide (XIX).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of II. The mixture was stirred and refluxed for 12 hr. and then hydrolyzed by method c. The insoluble material was removed by filtration, washed with ether, and recrystallized.

Diphenylbenzylphosphine Oxide (VIII).—Compound XIX (6.0 g.) and 60 ml. of a 15% solution of potassium hydroxide in ethanol were refluxed for 3 hr. The ethanol was removed, the residue (XX) was dissolved in water, and the solution was extracted with benzene. When the alkaline solution was acidified, carbon dioxide was evolved and VIII precipitated. After recrystallization from ethanol to yield was 1.0 g. (20%), m.p. and m.m.p. 190–192°, lit.[5–8] m.p. 192–193°.

N,N-Dimethylphenyl(diphenylphosphinothioyl)acetamide (XXI).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to a stirred suspension of II and the mixture was refluxed for 2 hr. Sulfur (6.4 g., 0.2 g.-atom), dissolved in 75 ml. of carbon disulfide, was added, dropwise, to the stirred mixture. The material was refluxed for 1 hr., then stirred for 3 hr. and hydrolyzed by method c. The organic layer was dried, the solvent removed, and the residue was washed with carbon disulfide.

N,N-Dimethylphenyl(diphenylphosphino)acetamide Methiodide (XXII).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to a stirred suspension of II. The mixture was refluxed for 2 hr., 28.4 g. (0.2 mole) of methyl iodide was added dropwise, the mixture was stirred for 12 hr. and then hydrolyzed by method c. The insoluble methiodide was removed by filtration, dissolved in ethanol, the solution was decolorized with Nuchar, filtered, and the solvent removed.

N,N-Dimethylphenyl(phenylhydroxyphosphinyl)acetamide (XXIV).—Phenyldichlorophosphine oxide (19.5 g., 0.1 mole) was added, dropwise, to a stirred suspension of II. The mixture was refluxed for 2 hr. and then hydrolyzed by method c. The oil which separated between the organic and the aqueous layer was removed and triturated with hot petroleum ether (b.p. 90–100°). The insoluble solid residue was dissolved in chloroform and the solution was extracted with aqueous sodium bicarbonate. The alkaline layer was acidified, extracted with chloroform, and the solvent was removed from the organic layer.