[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Organophosphorus Compounds. I. Derivatives of 3-Nitro-4-chlorophenylphosphonic Acid

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Since phosphorus lies just above arsenic in the periodic table, it was thought that the study of derivatives of phenylphosphonic acids, corresponding in structure to known arsonic acids[2] might be of interest from both a chemical and physiological point of view. This investigation, therefore, deals with certain derivatives of 3-nitro-4-chlorophenylphosphonic acid.

p-Chlorophenylphosphinic acid was prepared by the action of phosphorus trichloride on chlorobenzene in the presence of aluminum chloride and hydrolysis of the resulting *p*-chlorophosphenyl dichloride. A simultaneous oxidation and nitration of *p*-chlorophenylphosphinic acid with fuming nitric acid at 100° gave 3-nitro-4-chlorophenylphosphonic acid. This compound was identical with that obtained by Michaelis[3] by nitration of *p*-chlorophenylphosphonic acid.

The monosodium salt of 3-nitro-4-chlorophenylphosphonic acid condensed readily in aqueous solution with *n*-propyl, *n*-butyl, *i*-butyl, *n*-amyl, *i*-amyl, monoethanolamine and morpholine to give 3-nitro-4-N-alkylaminophenylphosphonic acids (Table I). An excess of the amine prevented the possible condensation of two moles of the acid with one mole of the amine to give 2,2′-dinitro-4,4′-diphosphonodiphenyl-N-alkylamines.

By reduction of the nitro compound with hydrogen at forty pounds pressure and Raney nickel[4] catalyst, the corresponding 3-amino-4-alkylaminophenylphosphonic acid was obtained. In all cases the aminophenylphosphonic acid melted much higher than the corresponding nitro compound, a fact previously noted by Michaelis[3] with similar compounds. Most of the nitrophenylphosphonic acids decomposed on melting and the aminophenylphosphonic acids behaved as amine salts.

Glycine condensed with 3-nitro-4-chlorophenylphosphonic acid under anhydrous conditions to yield 3-nitro-4-α-carboxymethylaminophenylphosphonic acid. Catalytic reduction did not give the free base 3-amino-4-α-carboxymethylaminophenylphosphonic acid but water was eliminated between the amine group and the carboxy group and 1,2,3,4-tetrahydro-3-oxo-6-quinoxalinephosphonic acid was obtained which was confirmed by the phosphorus analysis and the negative primary amine test. A similar ring closure has been noted with the corresponding arylarsonic acid.[2]

Phenol reacted with 3-nitro-4-chlorophenylphosphonic acid by heating the reactants in the presence of potassium carbonate and a trace of copper powder. *o*-Chlorophenol and *p*-chlorophenol condensed in isoamyl alcohol to yield derivatives of 3-nitro-4-phenoxyphenylphosphonic acid. Catalytic reduction of the nitro compound gave the corresponding 3-amino-4-phenoxyphenylphosphonic acid derivative.

By refluxing 3-nitro-4-chlorophenylphosphonic acid with 4 *N* sodium hydroxide, 3-nitro-4-hydroxyphenylphosphonic acid was obtained. Catalytic reduction gave 3-amino-4-hydroxyphenylphosphonic acid, which turns brown quickly in alkaline solution and darkens on exposure to air.

Experimental

p-Chlorophenylphosphinic Acid.—*p*-Chlorophenylphosphinic acid was prepared by a modification of the method of Michaelis.[3] The *p*-chlorophosphenyl dichloride was extracted from the reaction mixture with petroleum ether and, after removing the solvent by distillation, hydrolyzed to *p*-chlorophenylphosphinic acid. Two recrystallizations from water gave a white crystalline compound; yield 10%, m. p. 131°. Michaelis[3] reported 130–131°.

3-Nitro-4-chlorophenylphosphonic Acid.—*p*-Chlorophenylphosphinic acid was added slowly with stirring to an excess of fuming nitric acid (sp. gr. 1.52) heated over a water-bath. Dense brown fumes were given off and the solution was evaporated almost to dryness. Sufficient fuming nitric acid to dissolve the solid was added and the solution again heated over a water-bath until the solution evaporated almost to dryness. On cooling the phosphonic acid separated and was dried in a vacuum oven; yield 90%; m. p. 166°.

3-Nitro-4-N-alkylaminophenylphosphonic Acids.—3-Nitro-4-chlorophenylphosphonic acid (4.75 g.), 2 *N* sodium hydroxide (12 ml.), and the amine (5 ml.) were heated in a flask fitted with a condenser and stirrer for six to eight hours at 120°. The reaction mixture was evaporated to about 15 ml. and was made acid to congo red paper. The

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(2) Maclay and Hamilton, THIS JOURNAL, **54**, 3310 (1932).

(3) Michaelis, *Ann.*, **293**, 193 (1896).

(4) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

TABLE I

COMPOUNDS AND PROPERTIES

	Compound	Description[b]	M. p., °C.	Yield, %	Formula	Anal. P, %[a] Calcd.	Found
	-aminophenolphosphoric acid						
1	3-Nitro-4-*n*-propyl-	Yellow needles, oblique ext.	178–179 dec.	52	$C_9H_{13}N_2O_5P$	11.9	11.8
2	3-Nitro-4-*n*-butyl-	Yellow rods, oblique ext.	176–178 dec.	51	$C_{10}H_{15}N_2O_5P$	11.24	11.11
3	3-Nitro-4-*i*-butyl-	Yellow rods, oblique ext.	176–180 dec.	60	$C_{10}H_{15}N_2O_5P$	11.24	11.22
4	3-Nitro-4-*n*-amyl-	Yellow rods, parallel ext.	132–134	53	$C_{11}H_{17}N_2O_5P\cdot H_2O$	10.14	10.20
5	3-Nitro-4-*i*-amyl-	Yellow needles, parallel ext.	171–173 dec.	58	$C_{11}H_{17}N_2O_5P$	10.78	10.69
6	3-Nitro-4-β-hydroxyethyl-	Orange plates, parallel ext.	182 dec.	50	$C_8H_{11}N_2O_6P$	11.83	11.77
7	3-Amino-4-*n*-propyl-	White needles, parallel ext.	>200	74	$C_9H_{15}N_2O_3P$	13.48	13.35
8	3-Amino-4-*n*-butyl-		>200	79	$C_{10}H_{17}N_2O_3P$	12.70	12.68
9	3-Amino-4-*i*-butyl-	White powder	>200	78	$C_{10}H_{17}N_2O_3P$	12.70	12.73
10	3-Amino-4-*n*-amyl-	White needles, parallel ext.	>200	79	$C_{11}H_{19}N_2O_3P$	11.98	11.86
11	3-Amino-4-*i*-amyl-		>200	67	$C_{11}H_{19}N_2O_3P$	11.98	11.87
12	3-Amino-4-β-hydroxyethyl-	White needles, parallel ext.	>200	73	$C_8H_{13}N_2O_4P$	13.33	13.18
13	3-Nitro-4-morpholinophenylphosphonic acid	Orange prisms, anisotropic	176	33	$C_{10}H_{13}N_2O_6P$	10.76	10.71
14	3-Amino-4-morpholinophenylphosphonic acid	Brown powder	>200	50	$C_{10}H_{15}N_2O_4P$	12.01	11.87
15	3-Nitro-4-α-carboxymethylaminophenylphosphonic acid	Yellow rods, parallel ext.	>200	50	$C_8H_9N_2O_7P\cdot 2H_2O$	9.96	9.87
16	1,2,3,4-Tetrahydro-3-oxo-6-quinoxaline-phosphonic acid	White needles, parallel ext.	>200	76	$C_8H_9O_4N_2P$	13.59	13.51
	-phenylphosphonic acid						
17	3-Nitro-4-phenoxy-	Tan needles, parallel ext.	>200	57	$C_{12}H_{10}NO_6P\cdot 3H_2O$	8.87	8.91
18	3-Nitro-4-(*o*-chlorophenoxy)-	Tan isotropic, crystals	>200	22	$C_{12}H_9NO_5PCl\cdot H_2O$	8.92	8.91
19	3-Nitro-4-(*p*-chlorophenoxy)-	Tan isotropic plates	>200	36	$C_{12}H_9NO_6PCl\cdot 2H_2O$	8.48	8.37
20	3-Amino-4-phenoxy-	Gray needles, anisotropic	>200	58	$C_{12}H_{12}NO_4P\cdot 2H_2O$	10.30	10.34
21	3-Amino-4-(*o*-chlorophenoxy)-	White needles, parallel ext.	>200	80	$C_{12}H_{11}NO_4PCl\cdot 2H_2O$	9.27	9.41
22	3-Amino-4-(*p*-phenoxy)-	Gray needles, parallel ext.	>200	57	$C_{12}H_{11}NO_4PCl\cdot 3H_2O$	8.77	8.44
	-phenylphosphonic acid						
23	3-Nitro-4-hydroxy-	Isotropic crystals	214–216	78	$C_6H_6NO_6P\cdot H_2O$	13.09	12.98
24	3-Amino-4-hydroxy-	Brown needles, parallel ext.	>200	67	$C_6H_8NO_4P\cdot H_2O$	14.97	15.07

[a] Analysis for phosphorus was by the method of Neumann described in H. Meyer, "Analyse und Konstitutionermittelung organishen Verbindungen," Julius Springer, Berlin, 1909, p. 289. [b] Crystals were studied under a polarizing microscope.

phosphonic acid separated and was purified by two recrystallizations from water accompanied by treatment with activated charcoal.

3-Amino-4-N-alkylaminophenylphosphonic Acids.—The monosodium salts of the 3-nitro-4-N-alkylaminophenylphosphonic acids were reduced in aqueous solution using hydrogen at forty pounds pressure and Raney nickel[4] catalyst. After reduction was complete the catalyst was filtered off and the solution made acid to congo red paper. The 3-amino-4-N-alkylaminophenylphosphonic acid separated, was filtered off, washed well with water and dried.

3-Nitro-4-α-carboxymethylaminophenylphosphonic Acid.—3-Nitro-4-chlorophenylphosphonic acid (9.5 g.), glycine (5 g.), anhydrous potassium carbonate (9 g.), and isoamyl alcohol (30 ml.) were heated for nine hours at 145° in a flask fitted with a stirrer and a condenser. The iso-amyl alcohol was removed by steam distillation and the residual solution acidified to congo red paper. The phosphonic

acid separated and was purified by two recrystallizations from water accompanied by treatment with activated charcoal.

1,2,3,4-Tetrahydro-3-oxo-6-quinoxaline-phosphonic Acid.—When the monosodium salt of 3-nitro-4-α-carboxymethylaminophenylphosphonic acid was reduced with hydrogen and Raney nickel[4] catalyst the free base, 3-amino-4-α-carboxymethylaminophenylphosphonic acid, which was not isolated, lost water to form a quinoxaline derivative. 1,2,3,4-Tetrahydro-3-oxo-6-quinoxalinephosphonic acid which separated when the filtrate from the reduction was acidified to congo red paper, was filtered off, washed well with water and dried.

3-Nitro-4-phenoxyphenylphosphonic Acid.—3-Nitro-4-phenoxyphenylphosphonic acid was obtained by heating a mixture of 3-nitro-4-chlorophenylphosphonic acid (5 g.), anhydrous potassium carbonate (5 g.), phenol (10 g.), and a trace of copper powder, for nine hours at 125° with agitation. The excess phenol was removed by steam distillation. The phosphonic acid was precipitated with dilute hydrochloric acid and purified by two recrystallizations from dilute acetic acid accompanied by treatment with activated charcoal.

3-Nitro-4-(*o*-chlorophenoxy)-phenylphosphonic Acid and 3-Nitro-4-(*p*-chlorophenoxy)-phenylphosphonic Acid.—3-Nitro-4-(chlorophenylphosphonic acid (5 g.), anhydrous potassium carbonate (5 g.), isoamyl alcohol (15 ml.), copper powder (5 g.), and either *o*- or *p*-chlorophenol (2.5 g.) were heated at 145° for seven to nine hours in a flask fitted with a stirrer and a condenser. The isoamyl alcohol and excess phenol were removed by steam distillation. The phosphonic acid was precipitated with dilute hydrochloric acid and purified by two recrystallizations from dilute acetic acid accompanied by treatment with activated charcoal.

3-Amino-4-phenoxyphenylphosphonic Acid Derivatives.—The 3-nitro-4-phenoxyphenylphosphonic acid derivatives were reduced in the same manner as the 3-nitro-4-N-alkylaminophenylphosphonic acids to give 3-amino-4-phenoxyphenylphosphonic acid derivatives.

3-Nitro-4-hydroxyphenylphosphonic Acid.—3-Nitro-4-chlorophenylphosphonic acid was refluxed for four hours in 4 *N* sodium hydroxide solution. 3-Nitro-4-hydroxyphenylphosphonic acid separated slowly after the solution was made acid to congo red paper and was purified by recrystallization from water.

3-Amino-4-hydroxyphenylphosphonic Acid.—Catalytic reduction of 3-nitro-4-hydroxyphenylphosphonic acid in the same manner as the 3-nitro-4-N-alkylaminophenylphosphonic acids were reduced gave 3-amino-4-hydroxyphenylphosphonic acid which darkens quickly in air or in solution.

Summary

3-Nitro-4-chlorophenylphosphonic acid has been prepared and condensed with several aliphatic amines, namely, *n*-propyl, *n*-butyl, *i*-butyl, *n*-amyl, *i*-amyl and ethanolamines, morpholine and glycine. The corresponding amine derivatives of the condensation products were obtained by reduction except that of glycine which gave 1,2,3,4-tetrahydro-3-oxo-6-quinoxaline-phosphonic acid.

3-Nitro-4-chlorophenylphosphonic acid has been condensed with phenol, *o*-chlorophenol and *p*-chlorophenol to give phenyl ether derivatives. The aminophenyl ether derivatives have been prepared from the corresponding nitro compounds.

3-Nitro-4-hydroxyphenylphosphonic acid has been prepared and reduced to 3-amino-4-hydroxyphenylphosphonic acid.

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Vinyl Alcohols. II. 1,2-Dimesityl-1-propen-1-ol

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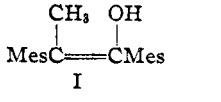
The vinyl alcohol 1,2-dimesityl-1-propen-1-ol (I, Mes = mesityl), described in the preceding communication,[3] is remarkable because it contains only hydrocarbon substituents. Most enolic compounds have a carbonyl group and are probably chelated. The enol form (II) of benzohydrylbenzoylacetomesitylene described by Kohler, Tishler and Potter[4] is an example of this type. The stability of certain enols cannot be explained in this way, however. The enol form (III) of benzyl phenyl diketone[5] has been shown by Kohler and Barnes[6] to behave as an unchelated hydroxy ketone. The possibility of ascribing the sta-



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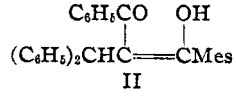

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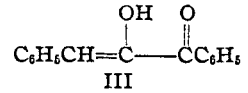
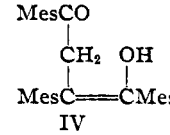


III



IV

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(4) Kohler, Tishler and Potter, *ibid.*, **57**, 2517 (1935).
(5) Moureu, *Ann. chim.*, [10] **14**, 303 (1930).
(6) Kohler and Barnes, THIS JOURNAL, **56**, 211 (1934).