grants from the Nutrition Foundation, and from the United States Public Health Service (Grant A-884). A gift of glycerol monochlorohydrin was made by Dr. W. F. Ross of Shell Development Company.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

The Base-catalyzed Reaction of Dialkyl Phosphonates with Isocyanates[1]

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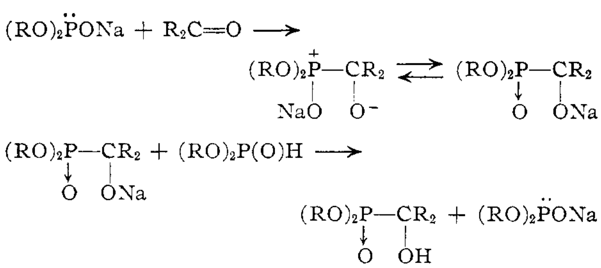
RECEIVED OCTOBER 10, 1955

A series of carbamoylphosphonates, $RNHCOPO(OR)_2$, has been prepared by the base-catalyzed reaction of isocyanates with dialkyl phosphonates.

In recent years, the addition of dialkyl phosphonates to unsaturated groupings such as carbonyl, imine or to activated carbon–carbon unsaturation has been extensively investigated.[2] These reactions are generally catalyzed by alkali metals or their alkoxides. Catalysis by other bases has not been reported.[3] It has been assumed that the mechanism of these reactions involves the polarization of the unsaturated group by the metal salt of the phosphonate, followed by addition of the dialkoxyphosphinyl radical. For example, reaction with ketones may take the course[4]



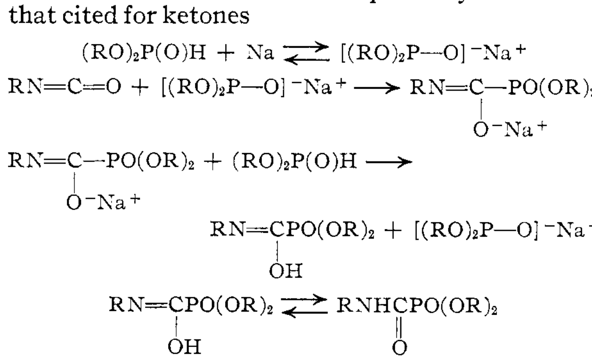
Since this course of reaction seems to be typical of the addition reactions of phosphonates, it would appear that the nucleophilic reactivity of the dialkoxyphosphinyl group, $(RO)_2P(O)^-$, would be better demonstrated through an addition reaction subject to general base catalysis.

The high reactivity of the isocyanate group toward nucleophilic reagents is well known.[5] Pseudo acids, such as aliphatic nitro compounds, have been shown to react with isocyanates in the presence of bases.[6] Indeed, dialkyl phosphonates themselves have been reported recently to react directly with aliphatic isocyanates in the absence of bases at temperatures on the order of 135°.[7] It would therefore seem probable that isocyanates and dialkyl phosphonates would react readily in the presence of bases to form carbamoylphosphonates.[7,8]

$$RNCO + HPO(OR)_2 \xrightarrow{\text{base}} RNHCOPO(OR)_2$$

This has indeed been found to be the case, and the reaction appears to be a general one. Not only the more reactive ethyl isocyanate, but aromatic isocyanates having varying substituents in the *para*-position react rapidly at room temperature with dialkyl phosphonates in the presence of catalytic quantities of strong bases such as sodium, sodium dialkyl phosphonates, triethylamine and cyclohexyldiethylamine. A less vigorous reaction takes place in the presence of weaker bases such as sodium carbonate, sodium cyanide, tributylamine or α-picoline; no catalysis was observed with dialkylanilines. Under our reaction conditions, little if any of the "spontaneous" reaction shown by Reetz, *et al.*,[7] took place.

At least in the case of sodium as catalyst, the mechanism of the reaction is probably similar to that cited for ketones



Since no significant changes were observed in the infrared spectra of mixtures of diethyl phosphonate and triethylamine, and since weak bases such as α-picoline were effective catalysts, an alternative mechanism may be operating. One such mechanism might involve an initial attack by the tertiary amine on the isocyanate, as proposed[9] for the base-

(1) Presented before the Division of Organic Chemistry at the 128th National Meeting of the American Chemical Society, Minneapolis, Minnesota, September, 1955.

(2) This work has been reviewed by A. N. Pudovik, *Uspekhi Khim.*, **23**, 547 (1954).

(3) A. N. Pudovik and L. I. Sidnikhina, *Zhur. Obshchei Khim.*, **24**, 1193 (1954), have indicated that no reaction takes place between O,O-di-*n*-butyl phosphonothioate and diethyl 2-propylidenemalonate in the presence of triethylamine, whereas a normal reaction takes place in the presence of sodium butylate to yield the addition product.

(4) V. S. Abramov, *Doklady Akad. Nauk., S.S.S.R.*, **73**, 487 (1950).

(5) H. Saunders and R. J. Slocumbe, *Chem. Revs.*, **43**, 203 (1948).

(6) R. N. Boyd and R. Leshin, THIS JOURNAL, **75**, 2762 (1953).

(7) T. Reetz, D. H. Chadwick, E. E. Hardy and S. Kaufman, *ibid.*, **77**, 3813 (1955).

(8) Using other synthetic routes, Reetz, *et al.*,[7] have described the series $RR'NCOPO(OC_2H_5)_2$, where R and R' are hydrogen or alkyl groups; B. A. Arbusov and N. I. Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 847 (1952), have prepared the series $(C_2H_5)_2NCOPO(OR)_2$ and $(C_2H_5)_2NCOPO(OR)C_2H_5$ (*ibid.*, 631 (1954)), where R is an alkyl group.

(9) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 9 (1949).

TABLE I
CARBAMOYLPHOSPHONATES, $R_1NHCOPO(OR_2)(OR_3)$

R_1	R_2	R_3	Yield,[a] %	M.p., °C.[c]	Analyses, %[b] Nitrogen Calcd.	Nitrogen Found	Phosphorus Calcd.	Phosphorus Found
α-$C_{10}H_7$	CH_3	CH_3	96	139.5–140.5	5.01	4.82	11.09	11.26
α-$C_{10}H_7$	C_2H_5	C_2H_5	95	95.5–97.5	4.55	4.54	10.08	10.12
α-$C_{10}H_7$	n-C_3H_7	n-C_3H_7	61	67.5–69.0	4.18	4.20	9.24	9.30
α-$C_{10}H_7$	i-C_3H_7	i-C_3H_7	64	102.1–102.5	4.18	4.20	9.24	9.40
α-$C_{10}H_7$	i-C_4H_9	i-C_4H_9	73	78.7–79.4	3.85	4.10	8.53	8.46
p-ClC_6H_4	C_2H_5	C_2H_5	90	80.5–81.5	4.80	4.87	10.62	10.44
p-ClC_6H_4	n-C_3H_7	n-C_3H_7	63	48–50	4.38	4.50	9.69	9.52
p-ClC_6H_4	i-C_3H_7	i-C_3H_7	69	128.0–128.7	4.38	4.46	9.69	9.77
p-ClC_6H_4	i-C_4H_9	i-C_4H_9	85	67–68	4.03	4.08	8.91	8.72
p-BrC_6H_4	C_2H_5	C_2H_5	77	90.5–92.0	4.17	4.23	9.22	9.14
p-BrC_6H_4	n-C_3H_7	n-C_3H_7	74	64.5–65.5	3.85	3.84	8.51	8.58
p-BrC_6H_4	i-C_3H_7	i-C_3H_7	48	134.5–135.5	3.85	4.02	8.51	8.52
p-BrC_6H_4	i-C_4H_9	i-C_4H_9	59	78–79	3.57	3.92	7.90	7.91
p-BrC_6H_4	C_2H_5	n-C_4H_9	28	46.5–47.2	3.85	3.96	8.51	8.58
p-$O_2NC_6H_4$	CH_3	CH_3	51	150.5–151.5	10.20	10.34	11.30	11.12
p-$O_2NC_6H_4$	C_2H_5	C_2H_5	36	144–145	9.28	9.40	10.25	10.40
p-$O_2NC_6H_4$	n-C_3H_7	n-C_3H_7	39	118.5–119.5	8.48	8.36	9.38	9.20
p-$O_2NC_6H_4$	i-C_3H_7	i-C_3H_7	35	144.4–144.8	8.48	8.56	9.38	9.48
p-$O_2NC_6H_4$	n-C_4H_9	n-C_4H_9	41	90.5–91.5	7.82	7.58	8.65	8.52
p-$O_2NC_6H_4$	i-C_4H_9	i-C_4H_9	22	121–122	7.82	7.80	8.65	8.62
p-$O_2NC_6H_4$	n-C_5H_{11}	n-C_5H_{11}	45	65.4–65.9	7.24	7.70	8.02	8.04
p-$O_2NC_6H_4$	C_2H_5	n-C_4H_9	41	86.4–86.8	8.48	8.53	9.38	9.41

[a] Based on 0.02-mole runs by method B using triethylamine as catalyst; product recrystallized once. [b] Oakwold Laboratories, Alexandria, Va. [c] Uncorrected.

catalyzed reaction between alcohols and phenyl isocyanate.[10]

Both liquid and solid carbamoylphosphonates were prepared; the solids are listed in Table I. With the exception of the product derived from ethyl isocyanate, the liquids could not be distilled without decomposition to the original reactants at temperatures on the order of 160° at 1 mm. pressure. In one instance, that of diethyl phenylcarbamoylphosphonate, the small recovery of product may have been due to actual distillation or to recombination of the decomposition products in the receiver. The solid arylcarbamoylphosphonates are well suited as characterizing derivatives for dialkyl phosphonates, since they may be prepared with only a small loss in yield in an open test-tube merely by mixing the reactants with a few drops of triethylamine or a small piece of sodium.

The solubility properties of the solid derivatives varied considerably with the size of the ester group. All were quite soluble in polar organic solvents and insoluble in water. With increasing ester chain length, solubility in both polar and non-polar solvents increased markedly. Petroleum ether was the most satisfactory recrystallizing solvent for the higher members of the series. Generally, isopropyl ether, cyclohexane or n-hexane were satisfactory solvents with which to separate the carbamoylphosphonates from the principal impurity, the diarylurea resulting from the hydrolysis of the isocyanate.

As stated by Reetz, *et al.*,[7] the carbamoylphosphonates are fairly stable in the presence of water. However, with the aryl derivatives, the course of hydrolysis in acid or base depends on the substituent present in the aryl group. Hydrolysis of the p-nitro derivatives takes place readily, with cleavage at the amide linkage and the formation of p-nitroaniline. The p-chloro and p-bromo derivatives, on the other hand, are completely soluble in cold 2% sodium hydroxide, and only after boiling and acidification with a large excess of acid is there precipitated a water-soluble acid containing nitrogen, phosphorus and halogen. The same material results on treatment of the esters with phosphorus pentachloride, followed by hydrolysis and acidification. These acids give consistently higher neutralization equivalents than predicted for the expected carbamoylphosphonic acids and are being further investigated. Attempts to prepare these acids from the esters with thionyl chloride were unsuccessful.

Aminolysis of the p-chlorophenylcarbamoylphosphonates leads to the expected cleavage of the phosphinyl moiety; reaction of the esters with n-butylamine results in fair yields of 1-n-butyl-3-p-chlorophenylurea.

Acknowledgment.—We wish to express our appreciation to Mr. L. W. Daasch for the interpretation of the infrared spectra and to Mr. John C. Goan for technical assistance.

Experimental

Materials.—The dialkyl phosphonates were commercial products or were prepared by conventional methods from phosphorus trichloride, the alcohol and triethylamine. Ethyl n-butyl phosphonate was synthesized by the transesterification method.[11] Isocyanates were Eastman Kodak products used without further purification, with the exception of p-nitrophenyl isocyanate, which was recrystallized from ligroin.

(10) The lack of catalysis by dialkylanilines is explained by steric hindrance in the attack of the amine on the isocyanate (ref. 9). However, we have found the equally sterically hindered cyclohexyldiethylamine to be an effective catalyst in our reaction; the base strength of the amine appears to be the controlling factor.

(11) G. M. Kosolapoff, THIS JOURNAL, **73**, 4988 (1951).

Dialkyl Arylcarbamoylphosphonates. A. Preparative Method.—A typical preparation is that of diisopropyl *p*-chlorophenylcarbamoylphosphonate. Under anhydrous conditions, a solution of 3.30 g. (0.022 mole) of *p*-chlorophenyl isocyanate in 10 ml. of dry *n*-hexane was rapidly added at 30° to a stirred solution of 3.32 g. (0.020 mole) of diisopropyl phosphonate and 0.005 g. (0.002 mole) of sodium in 20 ml. of *n*-hexane. The temperature rose to 40° in five minutes, and after ten minutes at this temperature, the mixture was refluxed 1.5 hours, filtered from a small amount of bis-(*p*-chlorophenyl)-urea (m.p. 275–280°) and the filtrate concentrated to give 4.4 g. (69%) of product, m.p. 122–127°; after several recrystallizations from *n*-hexane, the melting point was 128.0–128.7°. Nearly identical results were obtained with two drops of triethylamine in place of the sodium.

B. Method of Characterizing Dialkyl Phosphonates.—Most of the derivatives listed in Table I were prepared by the following method. Two drops of triethylamine were added to a solution of 3.28 g. (0.02 mole) of *p*-nitrophenyl isocyanate in 3.32 g. (0.02 mole) of di-*n*-propyl phosphonate at room temperature in an open test-tube with a thermometer as stirrer. The temperature of the stirred mixture rose rapidly to about 100°, and the solution became turbid; on cooling, the mixture solidified. Extraction with isopropyl ether gave a residue consisting mostly of yellow bis-(*p*-nitrophenyl)-urea, m.p. 300–305°. The extract gave 2.6 g. (39%) of light yellow needles of di-*n*-propyl *p*-nitrophenylcarbamoylphosphonate, m.p. 115–119°. After several recrystallizations from isopropyl ether, it has m.p. 118.5–119°. In this instance, the temperature rise is the largest observed in the preparation of any of the derivatives; usually, the temperature increases to about 40–60° for these quantities. Under these reaction conditions, yields are generally lower than obtained by method A, but can be markedly increased by the use of a 20–30% excess of the isocyanate since the principal impurity is the substituted urea formed by the hydrolysis of the isocyanate by atmospheric moisture. Yields are somewhat diminished by an excess of phosphonate, due to the high solubility of the products in the excess ester and consequent difficulties in isolation.

Diethyl Ethylcarbamoylphosphonate.—A small (approximately 20 mg.) piece of sodium was added to a mixture of freshly distilled ethyl isocyanate (7.5 g., 0.106 mole) and diethyl phosphonate (14.6 g., 0.106 mole). The temperature rose rapidly to 60° with cooling in an ice–salt-bath. After the initial reaction subsided, the mixture was heated at 70° for 5 minutes. Distillation gave 7.0 g. of product, b.p. 105–106° (0.45 mm.), $n^{20}D$ 1.4509, d_{20} 1.1313; 6.5 g. of diethyl phosphonate and 3.5 g. of ethyl isocyanate were recovered unreacted.

Anal. Calcd. for $C_7H_{16}NO_4P$: C, 40.19; H, 7.71; P, 14.81. Found: C, 41.12; H, 7.62; P, 14.61.

Effect of Catalysts.—As a qualitative indication of the effect of various bases as catalysts, 0.001 mole of each base was added to a solution of 0.01 mole each of diethyl phosphonate and *p*-chlorophenyl isocyanate at 30° under the conditions of method B. For each base, the observed maximum temperature or the temperature to which the mixture was heated before reaction set in is given in Table II. Approximately 65–75% yields of diethyl *p*-chlorophenylcarbamoylphosphonate, m.p. 80–81°, were obtained in each case.

TABLE II

EFFECT OF CATALYSTS ON 0.01-MOLE RUNS OF *p*-$ClC_6H_4NHCOPO(OC_2H_5)_2$

Catalyst	Obs. max. temp., °C.
Na (in $(C_2H_5O)_2P(O)H$)	95
Triethylamine	65
Cyclohexyldiethylamine	52
α-Picoline	40
Tri-*n*-butylamine	39
NaCN	65[a]
Na_2CO_3	90[a]

[a] Temperature at which reaction sets in, as evidenced by a rapid temperature rise of about 20°.

Hydrolysis of *p*-Nitrophenylcarbamoylphosphonates.—Diethyl *p*-nitrophenylcarbamoylphosphonate (0.50 g.) gave a clear orange-red solution in 5 ml. of 2% sodium hydroxide on warming to 40°. On boiling a few minutes, the solution deposited a quantitative yield (0.23 g.) of yellow needles of *p*-nitroaniline, m.p. 147.5–148.5° (from water). No solid material was formed on addition of an excess of hydrochloric acid to the filtrate. The same results were obtained with the di-*n*-pentyl ester.

After refluxing a mixute of 0.5 g. of the diethyl ester in 10 ml. of distilled water for 5 hours, complete solution was achieved. On cooling, the solution deposited only *p*-nitroaniline; evaporation of the acidic filtrate failed to yield the expected carboxyphosphonate.[12]

Boiling the diethyl ester in 5% hydrochloric acid, followed by neutralization with sodium hydroxide, similarly gave *p*-nitroaniline.

Hydrolysis of *p*-Chloro- and *p*-Bromophenylcarbamoylphosphonates.—After refluxing for 1 hour in distilled water or 5% hydrochloric acid, both diethyl *p*-chloro- and *p*-bromophenylcarbamoylphosphonate were recovered unchanged.

Diethyl *p*-bromophenylcarbamoylphosphonate (2.8 g.) was completely soluble in 20 ml. of 5% sodium hydroxide. After heating the solution to incipient boiling and cooling, 8 ml. of concd. hydrochloric acid was added to precipitate 2.0 g. of an acid, white needles (from benzene), m.p. 149.5° (gaseous decomposition). Neut. equiv. calcd. for $ClC_6H_4NHCOPO(OH)_2$: 236. Found: neut. equiv. (potentiometric method), 266. The same material was obtained from the diisopropyl ester.

No alkyl iodide was detected on treatment of these acids with hydriodic acid. Infrared analysis showed the —NHCOPO= group to be intact; qualitative elemental analysis indicated the presence of halogen, nitrogen and phosphorus. The instability of the acids was demonstrated by steadily increasing neutralization equivalents and slightly decreasing melting points on repeated recrystallizations from hydrocarbon solvents.

Reaction of Diethyl *p*-Chlorophenylcarbamoylphosphonate with Phosphorus Pentachloride.—A vigorous reaction ensued upon mixing equimolar amounts of the ester and phosphorus pentachloride. The resulting clear yellow oil could not be distilled without decomposition. However, hydrolysis of the oil, neutralization of the resulting oil with sodium hydroxide, and reacidification with a large excess of hydrochloric acid precipitated an acid, m.p. 150° (gaseous decomposition), neut. equiv. 273, apparently identical to the acid obtained by alkaline hydrolysis of the ester.

Refluxing the ethyl ester with a large excess of thionyl chloride for 0.5 hour, followed by addition of the mixture to ice-water, gave a quantitative recovery of the original ester.

Reaction of *n*-Butylamine with Diethyl *p*-Chlorophenylcarbamoylphosphonate.—A solution of the ester (0.50 g., 0.0017 mole) in *n*-butylamine (0.5 g., excess) was refluxed 5 minutes. After standing 2 hours, the resulting oil was solidified by trituration with petroleum ether and filtered to give 0.50 g. of crude material. Recrystallization from benzene gave 0.30 g. (80%) of 1-*n*-butyl-3-*p*-chlorophenylurea, m.p. 172.5–173°. A mixed m.p. with a sample of the urea prepared from *n*-butylamine and *p*-chlorophenyl isocyanate showed no depression.

Infrared Spectra.—Spectra of mixtures of 0.1–1.5 moles of triethylamine per mole of diethyl phosphonate were recorded in the 2–15 μ region on a Perkin–Elmer model 21 spectrophotometer. No significant differences were noted between the observed spectrum and that expected from an addition of the separate spectra of the two compounds.

WASHINGTON, D. C.

(12) P. Nylen, "Studien Über Organische Phosphorverbindungen," Thesis, Uppsala, 1930, p. 50, found the acid $HOCOPO(OH)_2$ or its esters to be unstable in neutral or acidic solutions.