103. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part III.* Reactions with Amines.*

By I. DOSTROVSKY and M. HALMANN.

The reactions of dimethyl, diethyl, and di*iso*propyl phosphorochloridate with aliphatic primary, secondary, and tertiary amines are of second order, the rate decreasing in going from the methyl to the di*iso*propyl ester. Increase of the dielectric constant of the solvent leads to a strong acceleration. Added salts have a similar effect. The reactions with amines show the effect of steric interference on the approach of the reagent to the phosphorochloridate. The reactions are " slow " in that they possess low apparent activation energies and low Arrhenius frequency factors. A number of new dialkyl *N*-substituted phosphoramidates have been prepared.

CONTINUING our investigations of the reactions of dialkyl phosphorochloridates with nucleophilic reagents we have examined the action on the ester of primary, secondary, and tertiary aliphatic amines and of aniline. The studies were directed at elucidating the effect of the structures of the reagents and also solvent and salt effects. A broad survey of the reactions of dimethyl, diethyl, and di*iso*propyl phosphorochloridate with a number of amines was carried out. The reactions of the di*iso*propyl ester with a small number of amines in a variety of solvents were then studied with greater precision in order to elucidate solvent and salt effects. The solvents used included dry methanol, *n*-heptane, benzene, acetone, nitrobenzene, nitromethane, acetonitrile, and dioxan. With the exception of those with tertiary amines, the reactions of dialkyl phosphorochloridates with amines are of second order. This fact is demonstrated clearly in Table 1.

TABLE 1. *Rate constants for the reactions of di*iso*propyl phosphorochloridate with di-*n*-butylamine in ethanol at* 25·1°.* (Second-order rate constants.)

Initl. concn. of $Cl{\cdot}PO(OPr^i)_2$, mole/l.	0·048	0·057	0·17
,, ,, amine, mole/l.	0·12	0·18	0·47
k_2, l. mole^{-1} sec.$^{-1}$	0·0055	0·0053	0·0054

* Similar results were obtained in acetone solution.

The reactions proceed according to the equation $2NHR'R'' + (RO)_2POCl = (RO)_2PO(NR'R'') + NHR'R'',HCl$, as is shown by the isolation (see p. 513) of the expected amides. Two moles of amine disappear for each mole of phosphorochloridate reacting, one mole being precipitated (in most cases) as the hydrochloride.

With triethylamine in benzene solution, di*iso*propyl phosphorochloridate reacts slowly ($k_2 = 0{\cdot}5 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ at 0°) but only one mole of amine reacts and is precipitated as the hydrochloride. The nature of the product containing the phosphorus was not established and no olefin could be detected in the reaction mixture.

The effect of structural variations within the phosphorochloridate is illustrated in Table 2, and the effect of changes in amine structure in Table 3.

Reference to Table 2 shows that the rates of the solvolytic reactions and of those with anions and amines are affected similarly by variations in the alkyl groups of the dialkyl phosphorochloridates. This point is discussed in Part IV (following paper).

It was found that a secondary reacts much more slowly than the corresponding primary amine. Further, it is evident that branching in the α-position has a strong inhibiting effect on the rate (compare *n*-, *sec.*-, and *tert.*-butylamine), indicating the operation of steric factors. Lastly, the slowness of reaction of aniline is in keeping with its weaker basicity.

It is generally accepted that the nucleophilic power of a reagent, at least in a group of similar reagents, is closely related to its base strength. Now the latter property is usually defined with respect to the hydroxonium ion as acid, whereas in our reactions the " acid "

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* Part II, preceding paper.

is the much bulkier phosphorochloridate. Brown and his school (cf. summary in *Science*, **1946**, **103**, 385) have shown that the relative base strength of a series of amines depends on the reference acid used for the comparison. When the reference acid is of small volume, the sequence of base strength approximates to that expected from the operation of the usual electronic effects. On the other hand, when the reference acid is bulky, the order of base strength is different and may be determined entirely by the degree of steric interference to the approach of the amine and acid. These considerations lead us to expect the sequence of base strength and nucleophilic power with respect to the chlorophosphonate to be : primary > secondary > tertiary amines, and also for variations in the alkyl group of primary or secondary amines : *n*- > *sec.*- > *tert.*-butyl. Reference to Table 3 shows that such is indeed the case. This steric factor is of, course, additional to the usual electronic factor determining the base strength. Amines which are weak with respect to hydrogen ion, through the operation of electronic effects, can only be weaker still with respect to the bulkier acid (cf. the case of aniline).

TABLE 2. *Reactions of dialkyl phosphorochloridates with di*-n-*butylamine in dry ethanol.* (Second-order rate constants, in l. mole^{-1} sec.$^{-1}$.) *

Phosphoro-chloridate	Rate constant, k_2, at :				E_A, kcal./mole	10^{-4} *PZ*, l. mole^{-1} sec.$^{-1}$
	−12·9°	0°	25°	39·6°		
Dimethyl	0·019 [a]	0·039 [a]	—	—	8	10
Diethyl	0·008 [a]	0·019 [a]	—	—	8	5
Di*iso*propyl	0·0007 [a]	0·0012 [a]	0·0055 [b]	0·0103 [b]	8·9	2·0

[a] Measured by conductometric method and of low precision (about ±20%). [b] Measured by titration of liberated acid and of higher precision (±2%).

* The activation energies are probably accurate to within 2 kcal., with a corresponding range for the *PZ* factor.

TABLE 3. *Reactions of di*iso*propyl phosphorochloridate with various amines in benzene.* (Second-order rate constants, in l. mole^{-1} sec.$^{-1}$ × 10^4.)

Amine	Method *	Temp. 25·1°	39·6°	63·8°
n-Butylamine	(*a*)	300	—	—
iso- ,,	(*b*)	660	—	—
sec.- ,,	(*b*)	—	120	—
tert.- ,,	(*b*)	—	2	—
Diethylamine	(*b*)	—	11	—
Di-*n*-butylamine	(*a*) (*b*)	6	11	20
Di-*sec.*- ,,	(*b*)	—	0·1	0·3
Aniline	(*a*)	—	0·02	—

* (*a*) By titration of liberated chloride. (*b*) By titration of liberated acid.

Somewhat similar results were obtained by Arnett, Muller, and Day (*J. Amer. Chem. Soc.*, **1950**, **72**, **5635**), who, studying the aminolysis of methyl acetate, observed that the rate for reaction with *sec.*-butylamine was 46 times slower than that with *n*-butylamine, and the reaction with *tert.*-butylamine was immeasurably slow. These values should be compared with our results, where the reactions of *sec.*- and *tert.*-butylamine with di*iso*propyl phosphorochloridate are respectively 5 and *ca.* 300 times slower than that of *n*-butylamine. The effect in the two reactions compared is in the same direction as above, but less pronounced in the phosphorus compounds.

These reactions can be described as " slow " reactions, having an Arrhenius frequency factor far lower than the calculated collision frequency. This is associated, as in other " slow " reactions, with an unduly low apparent activation energy. Inspection of Tables 2 and 3 shows that the effect of temperature is small.

In this respect the reactions are similar to Menschutkin reactions and to the reactions of benzoyl chloride with amines. The effect of the solvent is again similar to that observed in such reactions. The strong accelerating effect of solvents of high dielectric constant should be particularly noticed (cf. Table 4) : *e.g.*, the change from benzene to ethanol as solvent leads to a 9-fold, and that from benzene to nitrobenzene to a 100-fold increase in the rate. These values should be compared with the values of 11 and 35 for the corresponding effect of solvent changes in the reaction between ethyl iodide and trimethylamine (Grimm, Ruf, and Wolff, *Z. physikal. Chem.*, 1931, *B*, **13**, 301). The salt effects presented in Table 5 are also typical of such reactions.

TABLE 4. *Di*iso*propyl phosphorochloridate and di*-n-*butylamine : solvent effect.* ($k_2 \times 10^2$, in l. mole^{-1} sec.$^{-1}$.)

Solvent	Method	Temp. −12·9°	0°	25·1°	39·6°	63·8°	Dielectric constant
n-Heptane	(*b*)	—	—	0·017	—	—	4·3
Benzene	(*a*) (*b*)	—	—	0·06	0·11	0·20	2·28
Ethanol..................	(*a*)	0·07	0·12	0·55	1·2	—	25·8
Dioxan	(*a*)	—	—	0·8	—	—	2·28
Acetone..................	(*a*)	—	0·8	2·5	—	—	21·4
Nitromethane	(*b*)	—	—	4·0	—	—	39·4
Nitrobenzene	(*a*)	—	—	6·0	—	—	36·1
Acetonitrile	(*a*)	—	—	7·5	—	—	38·8

(*a*) By titration of liberated chloride. (*b*) By titration of liberated acid.

TABLE 5. *The reaction of di*iso*propyl phosphorochloridate with di*-n-*butylamine at 25° in the presence of added substances.*

Solvent	Amine, mole/l.	Ester, mole/l.	Added substance	k_2, l. mole^{-1} sec.$^{-1}$
Benzene	0·083	0·016	—	0·0005
Benzene	0·044	0·0089	NEt_3,0·18N	0·0005
Ethanol...............	0·12	0·048	—	0·0055
Ethanol...............	0·10	0·042	$(Pr^iO)_2PO(NBu^n{}_2)$, 0·04M	0·008
Ethanol...............	0·12	0·040	NH_2Bu_2Cl, 0·12M	0·015
Ethanol...............	0·047	0·020	$NaClO_4$, 0·2M	0·02
Ethanol...............	0·10	0·020	NH_4NO_3, 0·2M	0·07

EXPERIMENTAL

(M. p.s are uncorrected.)

Materials.—Phosphorochloridates were prepared as described in Part I (*loc. cit.*). Technical heptane was stirred for 3 days with distilled chlorosulphonic acid, washed successively with pure sulphuric acid, aqueous sodium hydroxide, and water, dried ($CaCl_2$), and distilled twice through a Vigreux column. It showed no appreciable absorption in the ultra-violet spectrum down to 2400 Å. Benzene of technical grade was distilled, the first portion being discarded. Ethanol was dried by the ethyl phthalate method (Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1106). Technical dioxan was refluxed with sodium and fractionated through a 30-cm. vacuum-jacketed column packed with Fenske glass helices. (This column was used also in all fractionations of materials described in this section.) Acetone (ACS grade) was distilled before use. Nitromethane (Eastman Kodak Co.) was distilled from phosphoric anhydride. Aniline (C. P., Baker's " Analysed ") was used without further purification. Diethylamine (Sharples) was dried (KOH) and fractionated.

n-, *iso*-, and *sec.*-Butylamine, di-*n*-butylamine, di-*sec.*-butylamine (Eastman Kodak) were dried (KOH) and fractionated. The last had b. p. 131°; Mailhe (*Compt. rend.*, 1905, **33**, 965) reported b. p. 132°/758 mm.

tert.-Butylamine, prepared according to Pearson, Baxter, and Carter (*J. Amer. Chem. Soc.*, 1948, **70**, 2290; *Org. Synth.*, **29**, 21), had b. p. 44—45°.

Preparation of Esters of N-*Substituted Phosphoramidic Acids* NR′R″·PO(OR)$_2$.—(a) *Dimethyl* NN-*di*-n-*butylphosphoramidate* (R = Me, R′ = R″ = Bu). Dimethyl phosphorochloridate (2·9 g.) and di-*n*-butylamine (5·2 g.), dissolved in dry ether (50 ml.), were left in a stoppered flask at room temperature for 2 days, the precipitate was filtered off, and the filtrate distilled, yielding the *ester* as a colourless oil, b. p. 157—159°/41 mm., n_D^{25} 1·4327 (2·5 g., 53%) (Found: C, 49·4; H, 10·1; N, 6·0; P, 12·8. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9; P, 13·1%).

(b) The corresponding *diethyl* ester was prepared analogously (58% yield), b. p. 104—106°/1 mm., n_D^{25} 1·4299 (Found: C, 54·5; H, 10·9; N, 5·2; P, 12·0. $C_{12}H_{28}O_3NP$ requires C, 54·5; H, 10·6; N, 5·3; P, 11·7%). Di-*n*-butylamine hydrochloride was isolated in 58% yield.

(c) *Diiso**propyl* NN-*diethylphosphoramidate* (R = Pr^i, R′ = R″ = Et). Di*iso*propyl phosphorochloridate (2·06 g.) and diethylamine (2·3 ml.), in benzene (30 ml.), were kept for 2 days. A precipitate of diethylamine hydrochloride was filtered off (1·1 g., 98%), m. p. 222—225°. The filtrate was fractionated to yield the *ester* as an oil (2·1 g.,), 86%, b. p. 52—61°/0·1 mm. (Found: C, 51·2; H, 10·5; N, 5·6. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9%).

(d) *Diiso**propyl* N-n-*butylphosphoramidate* (R = Pr^i, R′ = H, R″ = Bu^n). Di*iso*propyl phosphorochloridate (3·0 g.) and *n*-butylamine (3 ml.) in benzene (20 ml.) similarly gave *n*-butylamine hydrochloride, m. p. 210° (Found: Cl, 31·4. Calc. for $C_4H_{12}NCl$: Cl, 32·4%), and the *ester* as an oil (1·1 g., 27%), b. p. 99—101°/0·5 mm., n_D^{25} 1·4239 (Found: C, 51·1; H, 10·2; N, 6·9; P, 12·6. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9; P, 13·1%).

(e) *Diiso**propyl* N-iso*butylphosphoramidate* was similarly prepared, but cooling with ice was necessary at first; it was an oil (63% yield), b. p. 103·5—104°/1·5 mm. (Found: C, 51·4; H, 10·9; N, 5·9%). *iso*Butylamine hydrochloride, m. p. 167°, was also obtained (83%).

(f) The sec.-*butyl* analogue was similarly prepared. Addition of light petroleum to the reaction mixture precipitated *sec.*-butylamine hydrochloride (90%), m. p. 144—145°, and the filtrate afforded the ester (75% yield), b. p. 101°/2 mm., m. p. 20—30° (Found: C, 50·9; H, 10·8; N, 5·8%).

(g) Analogous methods afforded *tert.*-butylamine hydrochloride, m. p. 275—282° (91% yield), and *diiso**propyl* tert.-*butylaminophosphoramidate*, b. p. 107—112°/3 mm., m. p. 60—62° (83% yield) (Found: C, 50·6; H, 10·5; N, 5·9%).

(h) *Diiso**propyl* NN-*di*-n-*butylphosphoramidate* (R = Pr^i, R′ = R″ = Bu^n), a colourless oil, had b. p. 110—112°/2 mm., n_D^{25} 1·4272 (yield 27%) (Found: C, 56·8; H, 11·1; N, 5·1; P, 10·6. $C_{14}H_{32}O_3NP$ requires C, 57·3; H, 10·9; N, 4·8; P, 10·6%); and di-*n*-butylamine hydrochloride (98% yield) (Found: Cl, 20·7. Calc. for $C_8H_{20}NCl$: Cl, 21·5%) was also obtained.

(i) *Diiso**propyl* NN-*di*-sec.-*butylphosphoramidate*. Di*iso*propyl phosphorochloridate (2·86 g.) and di-*sec.*-butylamine (4·0 g.), in acetonitrile (16 ml.), were kept for 2 days at 65°, then added to water (50 ml.) and extracted with light petroleum (50 ml.). After being dried (Na_2SO_4) and distilled, the *ester* was obtained as a colourless oil, b. p. 84—88°/1·5 mm. (0·5 g., 12%) (Found: C, 56·9; H, 10·6; N, 4·4%). Attempts to prepare this ester in benzene solution failed, because of the slowness of reaction. The di-*sec.*-butylamine hydrochloride produced was easily soluble in benzene, but could be precipitated with light petroleum (Found: Cl, 21·0. Calc. for $C_8H_{20}NCl$: Cl, 21·4%). Its m. p. after drying *in vacuo* at 60° was 115—120°, scarcely changed by dissolution in ethyl methyl ketone and precipitation with light petroleum. A sample prepared by bubbling hydrogen chloride through a light petroleum solution of the base also melted at 117—119°. Mailhe (*Compt. rend.*, 1905, **33**, 965) reported the salt to be very hygroscopic and did not give a m. p.

(j) *Diiso**propyl* N-*phenylphosphoramidate*. Di-*n*-butylamine (16·8 ml.) was added slowly to diphenyl phosphorochloridate (14·2 g.) in dry ether (50 ml.) cooled by tap water. After 5 hours the precipitate was filtered off, and the filtrate, after being washed with water and dried (Na_2SO_4), afforded the *ester* as a slightly viscous oil (12·4 g., 69%), b. p. 170—173°/0·5 mm., n_D^{25} 1·5173 (Found: C, 66·2; H, 7·9; N, 4·1; P, 8·6. $C_{20}H_{28}O_3NP$ requires C, 66·4; H, 7·8; N, 3·9; P, 8·6%).

Kinetic Measurements.—The reactions of amines with phosphorochloridates were followed by finding the rates of formation of chloride ion (*a*) by titration and (*b*) conductometrically, and (*c*) the rate of disappearance of free amine acidimetrically.

(a) *Titration method.* Samples (3 or 5 ml.) of the reaction mixture were run into cold 95% ethanol containing sulphuric acid in slight excess over that required to neutralize the free amine, and the chloride ion titrated with silver nitrate electrometrically (Part I). Second-order rate constants were calculated from the formula $k_2 = [2{\cdot}303/t(b - 2a)] \log a(b - 2x)/b(a - x)$, where a and b are the initial concentrations of phosphorochloridate and amine, and x is the concentration of chloride ions at time t (see equation, p. 511).

The rate constants obtained in this way showed a marked upward drift. This is not surprising in view of the marked salt effect (see Table 5). The rate constants were extrapolated to zero reaction and are thus the values for solutions with negligible ionic strength.

The method as described is suitable for reactions in solvents in which the amine hydrochloride is soluble, such as ethanol, acetone (0·01M-solutions), and acetontrile. Di-*sec.*-butylamine hydrochloride was soluble in benzene. For other solvents or amines, where amine hydrochlorides were sparingly soluble, samples of the reaction mixture were pipetted into glass-stoppered tubes (for fast reactions) or sealed in ampoules and kept for given periods of time in the thermostats. The contents were then washed out into cold acidic ethanol and titrated. An example is given herewith :

*Reaction of di*iso*propyl phosphorochloridate* (0·0464M) *with di*-n-*butylamine* (0·141M) *in absolute ethanol at* 0·0°.

t, sec.	0	293	675	1093	1860	3198	10,520	11,450	∞
0·00966N-$AgNO_3$, ml.	1·69	2·58	4·00	5·38	7·80	10·41	18·49	19·10	23·52
$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$	—	10·1	11·9	12·7	13·6	13·4	13·8	14·2	—

(b) *Conductometric method.* This method was used only for reactions in ethanol to obtain approximate rate constants for fast reactions at low temperatures. The technique was as described in Part I (*J.*, 1953, 507). The conductivity of the mixture is very sensitive to traces of water, an effect which could only be overcome by considerably more elaborate technique than was used. In calculating the rate constants it was assumed that the conductivity was proportional to the concentration of amine hydrochloride. This assumption was checked by constructing calibration curves and found to be sufficiently accurate in the range of concentration used. Second-order rate constants were calculated from the observed values of the resistance by substitution in the equation for the second-order rate constant (above) the value $x = a(R/R_t)$, where R and R_t are the values of the resistance of the cell at the end of the run and at time t, respectively. When $\log 2(b/2aR - 1/R_t)/(1/R - 1/R_t)$ is plotted against time a straight line is obtained, the slope of which is equal to $k_2(b - 2a)/2{\cdot}303$. An example is given below.

*Reaction of di*iso*propyl phosphorochloridate* (0·00914M) *with di*-n-*butylamine* (0·0985M) *in dry ethanol at* 0·23°.

Time, min.	0	5	10	20	38	40	51	65	∞
Resistance, ohms	18,000	12,560	9870	7170	6020	4980	4380	3870	2035·3

From the slope of the line taken between 10 minutes and infinity the value of 0·0017 l. mole^{-1} sec.$^{-1}$ was obtained for k_2.

(c) *Acidimetric method.* The rate of reaction of amine could be observed acidimetrically. Samples of the reaction mixture (3 or 5 ml.) were run into a mixture of 20 ml. of acetone and 5 ml. of a standard solution of perchloric acid in dioxan. The amount of perchloric acid was calculated to be slightly in excess over the initial amount of the amine in the sample. The excess of acid was back-titrated with a standard solution of triethylamine in toluene, lacmoid being used as indicator. The presence of ethanol up to about 15% did not interfere. *s*-Diphenylguanidine (recrystallized three times from toluene), m. p. 147—148°, served as primary standard (Carlton, *J. Amer. Chem. Soc.*, 1922, **44**, 1469). Triethylamine was found not to react with dialkyl phosphorochloridates under the conditions of this titration.

This titration method was found to be the most convenient, since it could be easily used for reactions having a half-life as short as 1 minute at room temperature, and moreover was not disturbed by precipitation of amine hydrochloride. Two examples follow.

*Reaction of di*iso*propyl phosphorochloridate* (0·0412M) *with* iso*butylamine* (0·194M) *in benzene at* 25·1°.

t, sec.	0	27	55	82	119	
NH_2Bu^i, mole/l.	0·165	0·152	0·142	0·135	0·129	
k_2, l. mole^{-1} sec.$^{-1}$	—	0·063	0·066	0·067	0·067	Mean 0·066

*Reaction of di*iso*propyl phosphorochloridate* (0·0550M) *with di*-n-*butylamine* (0·1772M) *in absolute ethanol at* 0°.

t, sec.	0	330	1410	2275	2732	3615	5310	7550
$NHBu_2$, mole/l.	0·1677	0·1620	0·1435	0·1340	0·1220	0·1193	0·1097	0·0986
$10^4 k_2$, l. mole^{-1} sec.$^{-1}$	—	10·9	12·8	12·2	12·8	13·2	12·4	12·7

Mean $k_2 = 0{\cdot}00124 \pm 0{\cdot}0001$ l. mole^{-1} sec.$^{-1}$.

WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL.

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