5% rhodium on alumina was hydrogenated at 50° and an initial pressure of 52 p.s.i. In 15 hr. the amount of hydrogen absorbed was constant at 104% of theory. The catalyst was separated by filtering the mixture through a Dicalite mat and washed well with benzene. Following the removal of the solvents *in vacuo*, the colorless oil which remained was dissolved in 1 l. of acetone. To the solution was added, with stirring and ice cooling, over a 4-hr. period, 125 ml. of 8 *N* chromic acid in 4.3 *M* sulfuric acid.[19] A reaction temperature of 2–3° was maintained throughout the addition. The excess oxidant was reduced by adding 15 ml. of isopropyl alcohol and the mixture concentrated to a small volume at reduced pressure. About 750 ml. of water, 300 ml. of 4 *N* sulfuric acid, and 200 ml. of methylene chloride were added and the mixture stirred for 14 hr. The aqueous layer was separated, saturated with salt and extracted repeatedly with methylene chloride. The combined methylene chloride extracts were washed once with water, dried over sodium sulfate, and concentrated to a small volume on a steam bath. Last traces of the solvent were removed *in vacuo*. A solution of the residual brown oil in 20 ml. of methanol was chilled to Dry Ice temperature. The diketone which precipitated was separated by filtration through a Dry Ice-chilled filter funnel and washed three times with Dry Ice-chilled methanol. After drying in air, the product weighed 9.72 g. (26%), m.p. 33.0–34.2°. Two low-temperature recrystallizations from ether gave a constant-melting product which melted, after drying overnight at 0.03 mm. over concentrated sulfuric acid, at 35.2–37.2°. Prior to the drying treatment, the air-dried sample melted at 35.2–39°. A solution in pyridine, treated with methanolic ferric chloride,[36] gave an intense red-violet color; decaline-1,8-dione gave a similar color under these conditions. The infrared spectrum contained much more detail than those of decaline-1,8-dione and 2-*n*-butyrylcyclohexanone, whose bands were also not as sharp. In the neat supercooled liquid absorption occurred at 3.37 (s), 3.46 (s), 4.13, 4.43, 4.45, 4.62, 4.86, 5.11, and 5.37 (all weak), 5.68 (m) (cyclopentanone C=O, liquid state), 5.91 (s),[23a] 6.15 (s) (far less broad than the band in decaline-1,8-dione),[23a] 6.84 (m), 7.04 (m), 7.27 (s) (broad), 7.55 (m), 7.66 (s), 7.79 (m), 8.22 (s), 8.30 (s), 8.58 (w), 8.83 (m), 8.95 (m), 9.22 (m), 9.41 (w), 9.68 (m), 9.82 (w), 10.29 (w), 10.48 (w), 10.77 (m), 11.39 (m), 11.72 (w) (broad), 12.26 (s), 14.70 (m) (broad), and 15.31 μ (m) (broad); shoulders were evident at 2.83 (w), 2.86 (w), 2.96 (m), 3.03–3.08 (s), 3.14–3.26 (s), 3.58 (m), 3.68 (m), 3.78 (m), 3.97 (w), 5.51 (w), 5.82 (m), 5.87 (s), 6.04 (s), 6.87 (m), 7.38 (m), 7.88 (w), 8.06 (w), and 8.44 μ (m). The spectrum of a solution in carbon tetrachloride showed two sharp bands of medium intensity at 2.94 and 3.05 μ and an additional broad band at 3.20 μ (m). On diluting the solution these bands disappeared and were replaced by a weak plateau at 3.15–3.30 μ.

In another preparation the product was isolated, after oxidation of the diol, as its copper salt rather than as the crystalline diketone. In this way a 31% yield of copper derivative, m.p. 202.5–207°, was obtained. After three recrystallizations from hexane–methylene chloride, the black shiny crystals (on pulverizing, a gray-green powder was formed) melted at 211.0–211.4° (evac.). The hexahydroindane-1,7-dione, formed on decomposing the complex with dilute sulfuric acid, melted, after one low temperature recrystallization from methanol, at 37.2–38.5°.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.06; H, 7.88.

The 2,4-dinitrophenylhydrazone derivative was obtained as an orange powder after recrystallization from ethyl acetate, m.p. (evac.) 214.3–216.3° dec., $\lambda_{\max}^{\mathrm{EtOH}}$ 363 mμ (absorption characteristic of saturated ketone derivatives[38]), $\lambda_{\min}^{\mathrm{EtOH}}$ 300 mμ.

Anal. Calcd. for $C_{21}H_{20}N_8O_8$: C, 49.22; H, 3.93; N, 21.87. Found: C, 48.79; H, 4.13; N, 21.50.

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The Reaction between Amines and Ethyl Methylphosphonochloridate

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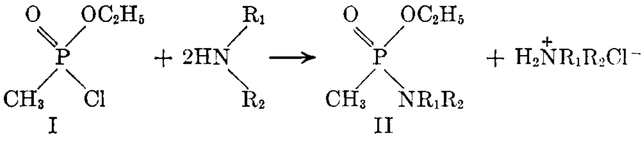
The kinetics of the reaction has been studied by use of a series of straight- and branched-chain amines; the results are consistent with an SN2 mechanism. The rate of reaction is highly influenced by steric effects as in many phosphorus substitution reactions. The products of the reaction, esters of N-substituted alkylphosphonamidic acids have been isolated and characterized.

The reaction between amines and phosphorus chlorides had not been closely studied prior to the detailed investigation by Dostrovsky and Halmann[2] on aminolysis of dialkyl phosphonochloridates. Razumov prepared a series of esters of N-substituted phosphonamidic acids by monoamination of phosphonochloridates followed by esterification, but the kinetics of the reaction was not studied.[3] In previous papers it has been shown that the structure of phosphonate esters has pronounced effects on their rates of hydrolysis,[4] and that the rate of alcoholysis of phosphonochloridate esters is greatly affected by structural changes in both the alcohol and chloridate molecules.[5,6] In all these reactions the main cause of the rate change is steric hindrance, the reactions having low entropy factors.



The reaction between phosphonochloridates (I) and amines to form N-alkyl phosphonamidate esters (II) demonstrates the role of this steric effect better than alcoholysis because both primary and secondary amines can be used to accentuate the steric effect of chain branching. Triethylamine did not react with the chloridate, while the reactions with ammonia, ethylamine, and *n*-butylamine were too fast to measure even at −50°. The rates of reaction between ethyl methylphosphonochloridate and a series of amines are shown in Table I, together with the Arrhenius parameters for the reactions. The order of reactivity (R = *sec*-butyl) is $NH_3 > RNH_2 > R_2NH$, the opposite of the order predicted from the inductive effects of alkyl groups on strength of organic bases, and in agreement with the results of Dostrovsky and Halmann. When amine

[1] Present address: Research & Engineering Division, Monsanto Chemical Co., St. Louis 66, Mo.

[2] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 511 (1953).

[3] A. I. Razumov, E. A. Markovich, and O. A. Kukhacheva, *Khim. i. Primenenie Fosfororgan. Soedin., Akad., Nauk SSSR Kazansk. Filial, Tr. l-oi Konf.*, 194 (1955); *Zhur. Obshch. Khim.*, **27**, 2389 (1954).

[4] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

[5] R. F. Hudson and L. Keay, *ibid.*, 1859 (1960).

[6] R. F. Hudson and L. Keay, *ibid.*, 1965 (1960).

TABLE I

RATES OF REACTION OF ETHYL METHYLPHOSPHONOCHLORIDATE WITH A SERIES OF AMINES, HNR_1R_2, IN ACETONE AND THE ARRHENIUS PARAMETERS FOR THE REACTION

(In all experiments the amine concentration is 0.05 N)

R_1	R_2	Chloridate, mole/l.	Temperature, °C.	k_2, l. mole^{-1} min.$^{-1}$	E_a cal./mole	ΔH^* cal./mole	ΔS^* e.u.	log PZ	Relative rate[a]
Et	Et	0.018	−12.2	18.4					
					3.9	3.4			
		.024	−25.0	12.4			−27.6	4.8	730
					4.6	4.1			
		.020	−34.0	8.32					
Bu	Bu	.019	−12.0	13.5					
					3.7	3.2			
		.022	−25.4	8.75			−28.6	4.6	540
					4.5	4.0			
		.020	−35.0	4.94					
sec-Bu	*sec* Bu	.015	25.8	0.0812					
					4.6	4.0			
		.013	12.0	.0560			−39.2	2.4	1
					5.2	4.7			
		.018	8.0	.0377					
tert-Bu	H	.021	0	7.25					
					4.4	3.9			
		.019	−9.8	5.35			−28.6	4.6	195
					5.3	4.8			
		.022	−25.0	2.99					
sec-Bu	H	.018	−48.7	3.71	...	...	...	...	≃900[b]
Ph	H	.014	44.5	0.124					
					8.1	7.5			
		.017	25.8	.0540			−30.5	4.2	057
					6.5	6.0			
		.018	0	.0213					

[a] Calculated at 0° by extrapolation. [b] Assuming E_a = 4.8 cal./mole.

basicity is measured potentiometrically, the inductive effect enhances the basicity except for the tertiary amine,[7] where steric repulsion between the three alkyl groups increases the bond angles from the 90° in ammonia to 108° in tertiary amines,[8] shielding the lone pair of electrons. When the alkyl groups are restrained in a ring reducing the shielding of the lone pair of electrons, the catalytic activity is increased.[9] Our results are similar to those of Brown and co-workers on the stability of the addition complexes formed between amines and trialkyl borons.[10] This steric repulsion between the amine alkyl groups (Brown's B strain) reduces the basicity and hence the nucleophilic reactivity of the base which could account for the slightly greater activation energy with di-*sec*-butylamine than with di-*n*-butylamine or diethylamine. The face-to-face interference between the bulky amine and the groups around the phosphorus atom during the formation of the bipyramidal transition state corresponds to Brown's F strain and is shown in the low entropy factor in the reaction with di-*sec*-butylamine. The entropy effect is like that recently observed with the substitution reactions of some polyfluoroalkyl halides.[11] It is possible that the F-strain is so great in the case of di-*sec*-butylamine that the bipyramidal transition state is distorted and that the nitrogen, phosphorus, and chlorine atoms can no longer become collinear, hence increasing the activation energy. The initial formation of an amine–phosphonochloridate complex followed by a rate-limiting breakdown of this complex is unlikely since the complex breakdown should not be so subject to steric hindrance and the reaction follows second order kinetics which also eliminates an SN1 mechanism. The slow reaction with the sterically unhindered aniline molecule which is a weaker nucleophile shows by its higher activation energy and unchanged entropy factor that the bond-forming step is rate-limiting.

The possibility has been considered that the amines are present in the reaction mixture as the *gem*-amino alcohol. But the equilibrium must lie well to the left or $k_b \gg k_f$ as second-order kinetics is accurately followed throughout the course of reaction. The negligible effect on this complex formation is further demonstrated by the effect of solvent change on the reaction rate (Table II). As was observed with the phosphonochloridates, there is not a direct relationship between

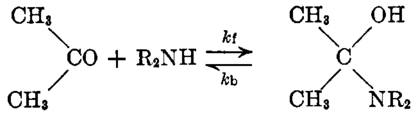


TABLE II

THE EFFECT OF SOLVENT ON THE RATE OF REACTION BETWEEN ETHYL METHYLPHOSPHONOCHLORIDATE AND *t*-BUTYLAMINE AT 11°

Solvent	Benzene	Dioxane	Acetone	Nitrobenzene	Nitromethane
Dielectric constant	2.28	2.28	21.4	36.1	39.4
k_2 l. mole^{-1} min.$^{-1}$	0.117	1.82	6.1[a]	16.5	13.2

[a] By extrapolation.

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(7) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441, 5444 (1957).

(8) L. O. Brockway and H. O. Jankins, *ibid.*, **58**, 2036 (1936).

(9) R. G. Pearson and F. V. Williams, *ibid.*, **76**, 258 (1954).

(10) H. C. Brown, *et al.*, *ibid.*, **64**, 325 (1941); **66**, 435 (1944); **67**, 1452, 1765 (1945); **75**, 1 (1953). *Science*, **103**, 385 (1946).

(11) E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Am. Chem. Soc.*, **84**, 3157 (1962).

the reaction rate and the dielectric constant of the medium.

The nature of the reaction has been demonstrated by the isolation of both the reaction products, the phosphonamidate esters (in 50–70% yield) and the amine hydrochloride (in 81–94% yield), and is a further example of the large part that steric effects play in the reactivity of quadruply connected phosphorus compounds.

Experimental[12]

Materials.—Acetone (Hopkin and Williams, AnalaR grade) was refluxed over anhydrous potassium carbonate for 6 hr. and then fractionated. The distillate was then refluxed over phosphoric oxide for 6 hr. and then fractionated, the fraction boiling at 56.0–56.5° being collected in a flask protected from atmospheric moisture by phosphoric oxide and calcium chloride guard tubes. Dioxane and nitrobenzene were purified using the methods described by Vogel.[13] Benzene (AnalaR grade) was refluxed over sodium and then fractionated. Nitromethane was dried over anhydrous magnesium sulfate and fractionated. Amines were dried over potassium hydroxide pellets, decanted from the solid and distilled from fresh potassium hydroxide pellets. Ethyl methylphosphonochloridate was prepared as described elsewhere.[4]

Determination of Reaction Rates.—A large, well insulated dewar vessel, containing water or aqueous acetone cooled with solid carbon dioxide was used as a constant temperature bath. The temperature was maintained within ±0.1° for at least 0.5 hr. The solution of the amine in the solvent was placed in a stoppered flask and precooled to the desired reaction temperature by placing the flask in the constant temperature bath. Reaction was started by introducing the phosphonochloridate from a weight pipet. The reaction flask was then shaken to ensure complete mixing. Five-milliliter portions were removed at suitable time intervals and added to acetone containing an excess of perchloric acid to stop the reaction as the alkylammonium ion formed does not react with the chloridate. The excess acid was then back titrated with a standard solution of triethylamine in toluene using Lacmoid indicator.

Isolation of Reaction Products.—A 1.42-g. sample (10 mmoles) ethyl methylphosphonochloridate was added slowly with stirring and cooling to 22 mmoles of the appropriate amine in 10 ml. of acetone. After 72 hr. at room temperature, 20 ml. of ether was added and the amine hydrochloride collected by filtration and washed with ether. The solvent was removed from the combined filtrate and washings, and the residue distilled under reduced pressure. The following compounds were prepared in this way.

Ethyl N-diethylmethylphosphonamidate (64% yield), b.p. 110–114°/22 mm. (Found: C, 46.5; H, 10.0; N, 8.0. $C_7H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-di-*n*-butylmethylphosphonamidate (75% yield), b.p. 108–110°/30 mm. (Found: C, 56.4; H, 11.8; N, 6.4; P, 14.1. $C_{11}H_{26}PO_2N$ requires C, 56.2; H, 11.9; N, 6.0; P, 13.2.)

Ethyl N-di-*sec*-butylmethylphosphonamidate (50% yield), b.p. 115–120°/30 mm. (Found: C, 55.5; H, 12.4; N, 5.4. $C_{11}H_{26}PO_2N$ requires C, 56.2; H, 11.9; N, 6.0.)

Ethyl N-*n*-butylmethylphosphonamidate (70% yield), b.p. 110–112°/20 mm. (Found: C, 45.9; H, 10.0; N, 7.2; P, 18.1. $C_{17}H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8; P, 17.3.)

Ethyl N-*sec*-butylmethylphosphonamidate (47% yield), b.p. 121–125°/30 mm. (Found: C, 47.5; H, 10.4; N, 7.5. $C_7H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-*tert*-butylmethylphosphonamidate (63% yield), b.p. 134–140°/25 mm. (Found: C, 46.8; H, 10.0; N, 6.8. $C_{17}H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-phenylmethylphosphonamidate (52% yield), b.p. 160–165°/20 mm. (Found: C, 55.0; H, 6.8; N, 7.3. $C_9H_{14}PO_2N$ requires C, 54.0; H, 7.0; N, 7.0.)

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[12] All melting points and boiling points are uncorrected.

[13] A. I. Vogel, "A Textbook of Practical Organic Chemistry," 2nd ed., Longmans, Green & Co., London, 1951, pp. 173–175.

The Reactions of α-Bromo Ketones with Primary Amines[1]

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The conversion of α-bromoisobutyrophenone to the corresponding α-hydroxyimines, I, II, and III has been effected in high yield by dissolution in liquid ammonia, methylamine, and ethylamine, respectively. Evidence is cited to support the intramolecular nature of the oxygen migration in the transformation which suggests a reaction path proceeding *via* an epoxyamine (IX) as an intermediate. Apparent anomolous pathways are observed in the reactions of α-bromopropiophenone and 6-bromo-2,2,6-trimethylcyclohexanone with liquid methylamine to yield 1-phenyl-1-methylaminoacetone and 6-methylamino-2,2,6-trimethylcyclohexanone, respectively.

The reactions of α-halo ketones with amines have received considerable attention in the chemical literature.[4] In general, it has been shown that α-halo ketones, whose structures prohibit a Favorskiĭ type rearrangement, undergo substitution and/or dehydrohalogenation where possible, upon treatment with ammonia, primary, or secondary amines.[4,5] Thus α,β-unsaturated ketones and α- and β-amino ketones have been observed as products of such reactions, the latter arising by 1,4-conjugate addition of the amine to the α,β-unsaturated ketone. Of particular interest in the present study is the behavior α-halo ketones toward ammonia and primary amines. The reaction of α-bromoisobutyrophenone with ammonia and methylamine in benzene or ethanol solution has been reported to yield mainly the products of substitution, α-amino-[6] and α - methylaminoisobutyrophenone,[7] respectively. The present work demonstrates that a variation of these reaction conditions can alter the course of the reaction to produce a heretofore unobserved product in high yield.

The dissolution of α-bromoisobutyrophenone in liquid ammonia followed by the gradual evaporation of the solvent led to a product which proved to be neither the result of elimination nor substitution. Elemental analysis indicated the crystalline product, isolated in 80% yield, was isomeric with the substitution product, α-aminoisobutyrophenone. The compound

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[2] Charles F. Kettering Foundation Fellow, 1958–1960; abstracted in part from the Ph.D. dissertation of P. Blumbergs, Wayne State University, 1962.

[3] Department of Chemistry, Arizona State University, Tempe, Ariz.; supported in part by a Parke, Davis and Co. Fellowship.

[4] See B. Tchoubar, *Bull. soc. chim. France*, 1363 (1955), for a review of the reactions of α-halo ketones with a variety of bases.

[5] N. H. Cromwell and P. H. Hess, *J. Am. Chem. Soc.*, **83**, 1237 (1961).

[6] H. Larramona, *Compt. rend.*, **232**, 849 (1951).

[7] C. Mannich and H. Budde, *Arch. Pharm.*, **271**, 51 (1933).