acts similarly to ATP in regard to chelation with Mg^{++} as observed in infrared spectra. However, Szent-Györgyi concludes that chelation with Mg^{++} is possible only with ATP and not with ADP, but the present results suggest that ATP and ADP form similar types of chelates. Since the first and second phosphate groups are common to both ATP and ADP, it suggests that these groups are involved in the complex formation. It is interesting to point out that not only does ATP require a divalent cation to transfer the terminal phosphate, but in enzymatic reactions in which ADP accepts a phosphate group[6] the divalent cation is again required for the operation.

The infrared evidence indicates the P–O–P and the purine nucleus are involved in the complex formation with Mg^{++} and that the two former groups should be within the same molecule; however, it does not clearly demonstrate whether the complexing is intramolecular or intermolecular. It is possible that the purine nucleus of one molecule can complex with the P–O–P of another through Mg^{++} and still maintain the 1:1 ratio of Mg^{++} to nucleotide. Either a dimer or a polymer could satisfy this condition and the present investigation does not clarify the point. It is hoped that future investigations will be able to determine whether the complexing is intra- or intermolecular.

SASKATOON, SASK., CANADA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, ETHYL CORPORATION]

The Synthesis of Alkyl Aryl Phosphates from Aryl Phosphorochloridates. I. The Sodium Alkoxide Route[1]

BY HAROLD D. ORLOFF, CALVIN J. WORREL AND FRANCIS X. MARKLEY

RECEIVED JULY 30, 1957

The synthesis of aryl phosphorodichloridates by the reaction of phenols with phosphoryl chloride is readily catalyzed by aluminum chloride. The yield of dichloridate is decreased by the presence of electron-withdrawing substituents such as chlorine in the aryl group. High yields of dialkyl aryl phosphates have been obtained by treating the dichloridate with sodium methoxide under controlled *p*H conditions. With excess of alkoxide, the product yield is reduced chiefly by an ester interchange reaction which yields trimethyl phosphate. The kinetics of the reactions of dialkyl aryl phosphates and trimethyl phosphates with sodium methoxide and sodium phenoxide are discussed.

Although phosphate esters have been the subject of intensive study for more than a century,[2,3] the preparation in high yield of mixed alkyl aryl phosphates presents a number of problems of interest from a synthetic, kinetic and mechanistic standpoint. Dialkyl aryl phosphates may be synthesized by the reaction of a phenol with a dialkyl phosphorochloridate, $(RO)_2POCl$, or of an alcohol with an aryl phosphorodichloridate, $ArOPOCl_2$, usually in the presence of a base or acid acceptor.

Of four methods considered[4] for the preparation of $(RO)_2POCl$, the reaction of an alcohol with phosphoryl chloride was found suitable for the formation of alkyl phosphorodichloridate, $ROPOCl_2$,[5,6] but not for the monochloridate. A more attractive route for the latter was stated to involve the reaction sequence

$$3C_2H_5OH + PCl_3 \longrightarrow (C_2H_5O)_2PHO + C_2H_5Cl + 2HCl \quad (1)$$

$$(C_2H_5O)_2PHO + Cl_2 \longrightarrow (C_2H_5O)_2POCl + HCl \quad (2)$$

wherein step 1 probably involves cleavage by hydrogen chloride of triethyl phosphite formed initially in the reaction.[7-9] A series of dialkyl aryl phosphates, hitherto unreported in the literature, except for diethyl *m*-tolyl phosphate, has been synthesized by this route in crude yields of 48–90%, based on dialkyl hydrogen phosphite (Table I). These preparations were carried out without distillation of the chloridate prior to reaction of the latter with aqueous sodium phenoxide. The low yields may be attributable in part to partial hydrolysis of the chloridate by the aqueous medium which would have the effect of removing $(RO)_2POCl$ in the form of the dialkyl hydrogen phosphate, $(RO)_2POOH$, and of liberating free phenol which was often difficult to remove from the product.

The Phosphorylation Reaction

In an attempt to achieve better utilization of phosphorus, avoid an aqueous system and eliminate the necessity for removal of free phenol from the products, the reaction series

$$ArOH + POCl_3 \longrightarrow ArOPOCl_2 + HCl \quad (3)$$

$$ArOPOCl_2 + 2ROH \longrightarrow (RO)_2(ArO)PO + 2HCl \quad (4)$$

was considered in detail. While a mixture of $ArOPOCl_2$, $(ArO)_2POCl$ and the triaryl phosphate, $(ArO)_3PO$, was expected from the phosphorylation reaction 3, the object of our study was to establish the effect of phenol structure, phosphoryl chloride to phenol ratio, reaction conditions and catalysts upon the yield of $ArOPOCl_2$.

---

(1) Presented before the Division of Organic Chemistry, 131st Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957.

(2) F. Vogeli, *Ann.*, **69**, 190 (1849).

(3) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 9.

(4) H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(5) J. Walczynska, *Roczniki Chem.*, **6**, 110 (1926).

(6) H. R. Gamrath, R. E. Hatton and E. Weesner, *Ind. Eng. Chem.*, **46**, 208 (1954).

(7) W. Gerrard, *J. Chem. Soc.*, 1464 (1940).

(8) An alternate route, $PCl_3 + 2C_2H_5OH + H_2O \rightarrow (C_2H_5O)_2PHO + 3HCl$, has been the subject of several patents, *e.g.*, H. Coates, British Patent 684,835, Dec. 24, 1952.

(9) P. W. Gann and R. L. Heider, U. S. Patent 2,692,890, Oct. 26, 1954.

TABLE I

DIALKYL ARYL PHOSPHATES SYNTHESIZED FROM SECONDARY ALKYL PHOSPHITES

$(RO)_2(ArO)PO$ R	Ar	Crude yield, %	Distilled at B.p., °C.	Distilled at Mm.	B.p., °C. (20 mm.)	Analyses (wt. %) Calcd. P	Calcd. Cl	Found P	Found Cl	$n^{20}D$
Me	Phenyl	77	114	2.0	159.0	15.4		15.6		1.4887
Me	*m*-Tolyl	63	113–115	1.0	171.0	14.4		14.5		1.4910
Me	*p*-Tolyl	85	114	0.5	172.2	14.4		14.2		1.4896
Me	3,5-Dimethylphenyl	61	125	1.2	177.0	13.5		13.5		1.4946
Me	*p*-(1,1,3,3-Tetramethylbutyl)-phenyl	48	160–165	0.7	217	9.9		9.9		1.4912
Me	*m*-Chlorophenyl	63	134	2.5	179.0	13.1	14.9	13.1	15.1	
Me	*p*-Chlorophenyl	54	108–110	0.5	176.0	13.1	14.9	12.9	15.1	1.5033
Me	4-Chloro-3-methylphenyl[a]		131	0.75	189.5	12.4	14.1	12.3	14.0	1.5074
Et	*m*-Tolyl[b]	57	124–126	1.0	178.2	12.7		12.6		1.4814
Et	*o*-Chlorophenyl	84	134	2.5	179.0	11.7	13.4	11.6	13.3	1.5026
n-Pr	*m*-Tolyl	52	146–148	1.0	191.0	11.4		11.3		1.4779
n-Bu	Phenyl	90	136–140	0.3	200	10.8		10.7		1.4736

[a] Prepared by direct phosphorylation of 4-chloro-3-methylphenol (run included for b.p. data). [b] A 96% yield ($n^{17}D$ 1.472) from diethyl phosphite and *m*-cresol, in the presence of triethylamine and with carbon tetrachloride as a solvent, has been reported by G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 524 (1955).

Influence of Catalysts.—Whereas *m*-cresol and phosphoryl chloride must be heated above 200° for 5–6 hours to carry out reaction 3, the addition of as little as one mole per cent. of aluminum chloride, based on the phenol, made it possible to complete the reaction in 40–50 minutes at 105°. To favor formation of the dichloridate, the cresol was added dropwise to the preheated $POCl_3$–$AlCl_3$ mixture. At temperatures below 90° the reaction rate dropped off considerably as measured by titration of hydrogen chloride evolved as a function of time. For example, at 60°, the reaction was only 80% complete in 90 minutes. At the latter temperature, with a phosphoryl chloride:*m*-cresol ratio of 1.2, the ratio of $ArOPOCl_2$:$(ArO)_2POCl$ obtained by rectification *in vacuo* was 13.3. At 40°, this ratio decreased to 2.6. Presumably because of the very low reaction rate, the concentration of unreacted cresol built up with the result that the average phosphoryl chloride:cresol ratio was appreciably lower than at 60°. Phosphorylations performed at moderately high temperatures did not give detectable differences in the yield of $ArOPOCl_2$. Because of the low boiling point of phosphoryl chloride, even at equimolar ratios with cresol, the initial temperature was limited to 105°. However, in one run the temperature was increased as rapidly as the vapor pressure of the mixture permitted with the result that at least half of the cresol addition was carried out at 120–130°. The yield of dichloridate was identical with that obtained in a 90° run.

Clean aluminum turnings have been employed in place of aluminum chloride. To produce active catalyst, the turnings were refluxed several hours with phosphoryl chloride. Aluminum cresoxide, prepared by heating the metal turnings with cresol at 150 to 200° until hydrogen evolution ceased, has also been used as a catalyst. A preferred method involved the preparation of the cresoxide in a small quantity of cresol, which was then fed to the phosphoryl chloride in a short time, followed by pure cresol.

Other catalysts have been reported in the literature,[10,11] including metal halides, iodine and ultraviolet light. We have investigated magnesium and zinc dust, magnesium and zinc chlorides, phosphorus trichloride and the highly acidic protonated acids, trichloroacetic and *p*-toluenesulfonic acids, as possible catalysts. Of these, only magnesium chloride and phosphorus trichloride gave evidence of accelerated reaction rates. With magnesium chloride, however, two mole per cent. of catalyst required 3 hours at 90° to give 95% of the theoretical amount of hydrogen chloride as compared with 40-50 minutes for aluminum chloride. The yield of *m*-tolyl phosphorodichloridate was slightly lower (87%) than that (92%) with aluminum chloride.

The metal halide-catalyzed reaction is quite sensitive to moisture which is frequently introduced in the starting phenol. Experiments carried out with various quantities of added water indicated that the reaction proceeds at a satisfactory rate if the water:aluminum chloride weight ratio does not exceed 0.2 (water:aluminum chloride mole ratio 1.6). At a weight ratio of about 0.28 (mole ratio 2.1) the catalyst was rendered inactive. The effect of moisture in the reaction was overcome by increasing the catalyst concentration.

If the ratio $ArOPOCl_2$:$(ArO)_2POCl$:$(ArO)_3PO$ were due to an equilibrium, that is, subject to thermodynamic control, the possibility of changing this ratio by kinetic control (selection of other catalysts, for example) would be small. A mixture of 0.5 mole of triphenyl phosphate, 1.5 moles of phosphoryl chloride and 0.015 mole of aluminum chloride was refluxed for 2.5 hours with no apparent change in the liquid phase temperature, 110.0–110.5°. The reaction product was distilled at 100 mm. (35–50° pot temperature) with recovery of 309.8 g. (97.5%) of the phosphoryl chloride in a trichloroethylene–Dry Ice trap at −70°. Upon reduction of the pressure to 0.8 mm. no additional distillate came over, even when the pot temperature was raised to 190°. These conditions were adequate for removal of phenyl phosphorodichloridate or of diphenyl phosphorochloridate if any had been present. Although this experiment indicated that an equilibrium of the type

$$(PhO)_3PO + POCl_3 \rightleftarrows PhOPOCl_2 + (PhO)_2POCl$$

---

(10) E. C. Britton, U. S. Patent 2,033,918, March 17, 1936.

(11) W. P. Ter Horst, U. S. Patent 1,840,335, January 12, 1932.

TABLE II

EFFECT OF PHOSPHORYL CHLORIDE:PHENOL RATIO ON THE CONVERSION OF PHENOL TO MONOARYLPHOSPHORODICHLORIDATE

Phenol	Ratio, $POCl_3$:phenol	Boiling points $ArOPOCl_2$ °C.	Mm.	$(ArO_2)POCl$ °C.	Mm.	Conversion mole %, phenol to $ArOPOCl_2$
Phenol	1.2	99.5–101.5	5			75.8
m-Cresol	1.2	124.5–125.5	10	173	1.7	77.7
		89–91	1	160–163	1	
m-Cresol	2.0					89.2
p-Cresol	2.0	90–91	1	166–170	1.25	85.5
3,5-Dimethylphenol	2.0	82–83	0.5	162–163	0.6	86.0
p-Chlorophenol	2.0	96–104	1–1.5			75.4
4-Chloro-3-methylphenol	2.0	79–82	0.1	155–157	0.1	83.4
o-Nitrophenol	2.0	150.2	2.8			52.2

did not occur under the conditions of temperature and catalyst concentration employed for the phosphorylation reaction 3, the data do not exclude such an equilibration at higher temperatures. The effectiveness of aluminum chloride eliminated the incentive to investigate other possible catalysts beyond the extent reported above.

Effect of Phosphoryl Chloride:Phenol Ratio.—Audrieth and Toy[12] have investigated the effect of reactant ratio in the presence of pyridine at −2°. Their results, determined after ammonolysis of the product, indicated that the yield of phenyl phosphorodichloridate increased with an increase in phosphoryl chloride:phenol ratio. Our data are in substantial agreement with these observations.

A series of phosphorylations was carried out with phenol, *m*- and *p*-cresol, 3,5-dimethylphenol, *p*-chlorophenol and 4-chloro-3-methylphenol, using one mole per cent. of aluminum chloride (based on phenol) as the catalyst. In each run the phosphoryl chloride and catalyst were heated to 90–100° and the phenol then was introduced over 0.5 hour with the temperature being allowed to rise as rapidly as possible to 105°. The course of the reaction was followed by absorption of the hydrogen chloride evolved and continuous titration with standard alkali. Table II summarizes the data obtained for a series of substituted phenols at various phosphoryl chloride:phenol ratios. Each of the values given in the last column represents the average molar yield of dichloridate (based on phenol charged) from a number of runs. Figure 1, representing a plot of the experimental results for *m*-cresol, 4-chloro-3-methylphenol and *p*-chlorophenol, indicates that the yield of dichloridate levels off at a ratio of about 2.

From these experimental data comparisons of results obtained at the same phosphoryl chloride: phenol ratio indicate that the presence of a methyl group in the aromatic ring has no appreciable electronic effect on the yield of dichloridate. With a *p*-chloro substituent, however, the yield was significantly lower, 75.4%, as compared with 85.5% for *p*-cresol at a 2:1 ratio of phosphoryl chloride: phenol. This may be attributed to the electron-withdrawing effect of the halogen atom. With a more strongly electron-withdrawing nitro group, as in *o*-nitrophenol, an even lower yield, 52.2%, was obtained. Whether the latter value may to some extent be attributable to steric influences cannot be stated on the basis of the limited data available. An attempt to employ *p*-nitrophenol under comparable reaction conditions was not successful owing to the high melting point of the *p*-nitro isomer. With both chloro and methyl substituents in the aromatic ring, as in 4-chloro-3-methylphenylphenol, the effect of halogen was nullified.

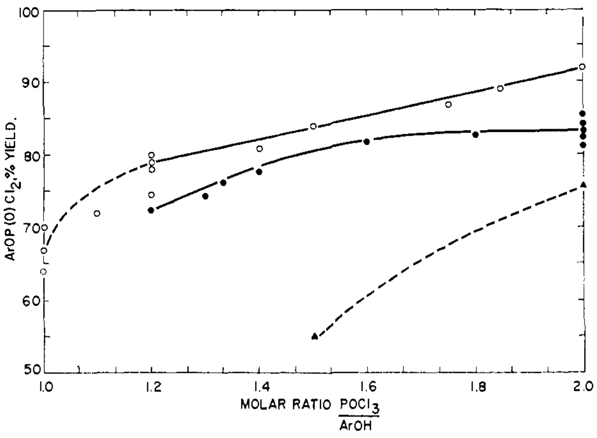


Fig. 1.—The effect of molar ratio of phosphoryl chloride to phenol upon the yield (mole per cent. based on phenol) of aryl phosphorodichloridate, $ArOPOCl_2$. Symbols for Ar: o, *m*-tolyl; ●, 4-chloro-3-methylphenyl; ▲, *p*-chlorophenyl.

Composition of Phosphorylation Product.—Because of the appreciable difference in volatility, as indicated by the boiling point data in Table II, separation of the dichloridate from the monochloridate was achieved readily. A number of these products were redistilled to at least 99% or better purity in order to establish analytical techniques[13] for determining the composition and purity of products from the phosphorylation reaction and to confirm the yields of dichloridate as derived from the distillation data. The analytical method involved hydrolyzing residual phosphoryl chloride with cold water and determining the resulting inorganic phosphoric acid gravimetrically. The aryl chloridates were hydrolyzed by refluxing with water and determined by potentiometric titration after correcting the strong and weak acid breaks for inorganic phosphoric acid derived from the phosphoryl chloride. Good agreement be-

---

[12] L. F. Audrieth and A. D. F. Toy, THIS JOURNAL, 63, 2117 (1941).

[13] We are indebted to Dr. M. E. Griffing and M. Brandt for the development of analytical procedures for analyzing phosphorylation reaction mixtures.

tween these data and those obtained in distillation of the phosphorylation products provides evidence that redistribution did not take place during the fractionation procedure.

In several cases the phosphorylation mixture was esterified directly without prior separation of dichloridate and monochloridate. To facilitate calculating the proper quantities of reactants for the esterification, total replaceable chlorine was first determined by addition of a small sample of the phosphoryl chloride-free mixture to an excess of methanol, followed by titration to *p*H 7 (or to a phenolphthalein end-point) with standard sodium methoxide solution or with aqueous caustic.

Esterification Reaction: The Sodium Alkoxide Route

Three simple methods for converting aryl phosphorochloridates to alkyl aryl phosphates are available. These involve treating the chloridate with an alcohol in the presence of an organic base, with sodium alkoxide or with the alcohol alone. Despite its general utility the first route was not investigated because of purification problems. The second and third[14] methods were investigated in detail.

The reaction between the dichloridate (or monochloridate) and sodium alkoxide may be accomplished by adding the former to an alcoholic solution of the alkoxide, by addition of the alkoxide to the dichloridate, or by simultaneous mixing of both reactants, with the feed controlled in order to ensure that neither reactant is present in excess.

The synthesis of alkyl aryl phosphates by addition of the alkoxide to the dichloridate is actually a variation of the reaction between the dichloridate and the alcohol alone. After the introduction and consumption of a portion of the alkoxide, free alcohol is present and reacts directly with the dichloridate, at the same time liberating hydrogen chloride which may reduce the yield by cleavage[14] of the ester unless the temperature and reaction time are controlled. Owing to the relatively large quantity of heat evolved from the use of sodium alkoxide, good control of temperature and high yields are not readily achieved by this method.

The addition of aryl phosphorodichloridate to an excess of sodium alkoxide, for example, gives low yields of the desired dialkyl aryl phosphate

$$\mathrm{ArOPOCl_2 + 2RONa \longrightarrow (RO)_2(ArO)PO + 2NaCl} \quad (5)$$

as a result of a series of side reactions. At the same time the dichloridate may undergo solvolysis with the alcohol solvent at a slower rate than (5) but with the same net effect. The side reactions encountered have been subjected to kinetic and product analysis in order to ascertain their nature and relative importance in the over-all process. Three alternative paths may be visualized for the system sodium methoxide–dimethyl phenyl phosphate

$$\mathrm{(CH_3O)_2(PhO)PO + CH_3ONa \longrightarrow (CH_3O)_3PO + PhONa} \quad (6)$$

$$\mathrm{(CH_3O)_2(PhO)PO + CH_3ONa \longrightarrow (CH_3O)_2POONa + PhOCH_3} \quad (7)$$

$$\mathrm{(CH_3O)_2(PhO)PO + CH_3ONa \longrightarrow (CH_3O)(PhO)POONa + CH_3OCH_3} \quad (8)$$

In experiments carried out at approximately room temperature, well over 95% of the dialkyl aryl phosphate underwent ester interchange *via* (6) to form trimethyl phosphate and sodium phenoxide. Within the limits of detection by infrared analysis, no evidence could be found for the presence either of anisole (7) or of dimethyl ether (8).

Since, during the course of (6), two bases, sodium methoxide and sodium phenoxide, are present at any stage between the beginning and end of the reaction, as well as two esters, it was of interest to investigate other possible mechanisms and products, and to compare their relative rates. The action of sodium methoxide upon trimethyl phosphate can lead only to sodium dimethyl phosphate and dimethyl ether

$$\mathrm{(CH_3O)_3PO + CH_3ONa \longrightarrow (CH_3O)_2POONa + CH_3OCH_3} \quad (9)$$

while sodium phenoxide and trimethyl phosphate give sodium dimethyl phosphate and anisole

$$\mathrm{(CH_3O)_3PO + PhONa \longrightarrow (CH_3O)_2POONa + PhOCH_3} \quad (10)$$

With dimethyl phenyl phosphate and sodium phenoxide, alternatives 11 and 12 at first were

$$\mathrm{(CH_3O)_2(PhO)PO + PhONa \longrightarrow (CH_3O)_2POONa + PhOPh} \quad (11)$$

$$\mathrm{(CH_3O)_2(PhO)PO + PhONa \longrightarrow (CH_3O)(PhO)POONa + PhOMe} \quad (12)$$

considered as more probable than (13)

$$\mathrm{(CH_3O)_2(PhO)PO + PhONa \longrightarrow (CH_3O)(PhO)_2PO + CH_3ONa} \quad (13)$$

because the latter process involves proceeding from a weaker to a stronger base. Careful examination of the reaction products failed to reveal the presence of diphenyl ether; anisole was the only ether detected spectrophotometrically. This result is strong evidence for (12) as the reaction path taken.

The kinetics of reactions 6, 9, 10 and 12 (or 13) were investigated to ascertain their relative rates. The reaction of sodium methoxide with both dimethyl phenyl phosphate and trimethyl phosphate, as well as the reaction between sodium phenoxide and trimethyl phosphate were found to give good values for second-order reactions as calculated by the usual rate expression. However, in the case of dimethyl phenyl phosphate and sodium phenoxide, reaction rate constants calculated from the expression for second-order kinetics decreased with time from *ca.* 1.7×10^{-5} liter mole^{-1} sec.$^{-1}$ at about 5% reaction of the base to approximately 1.2×10^{-5} liter mole^{-1} sec.$^{-1}$ at about 15% reaction. This unexpected result raises the possibility of a more complex mechanism than that given by (12). On the basis of the reaction rate constants at 42–43°, and using the value 1.7×10^{-5} liter mole^{-1} sec.$^{-1}$ for (12), the relative rates of reactions 6, 9, 12 and 10 are 670:6.7:2:1. Table III summarizes the kinetic data obtained, which represent the data from runs showing the best fit with the Arrhenius equation $k = Ae^{-E/RT}$.

The fact that dimethyl phenyl phosphate reacts about one hundred times more rapidly than does trimethyl phosphate with sodium methoxide and with an Arrhenius activation energy lower by 9

---

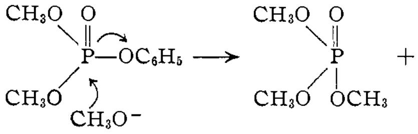
[14] H. D. Orloff, C. J. Worrel and F. X. Markley, THIS JOURNAL, **80**, 734 (1958).

TABLE III

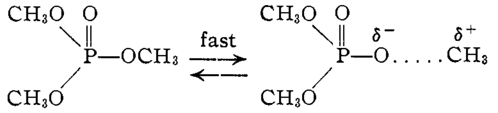
KINETIC DATA FOR THE REACTION OF SODIUM METHOXIDE AND PHENOXIDE WITH DIMETHYL PHENYI PHOSPHATE AND WITH TRIMETHYL PHOSPHATE IN ANHYDROUS METHANOL

Ester	Base	Temp., °C.	10^6k, l. mole^{-1} sec.$^{-1}$	E, kcal./mole	log A	$\Delta S\ddagger$, e.u.
$(CH_3O)_2(PhO)PO$	CH_3ONa	0.07	180			
		10.04	454	14.3	9.47	−25.2
		19.01	993			
$(CH_3O)_3PO$	CH_3ONa	25.00	6.66			
		33.81	21.5	23.3	15.47	− 6.0
		42.70	60.4			
$(CH_3O)_3PO$	PhONa	43.50	9.1			

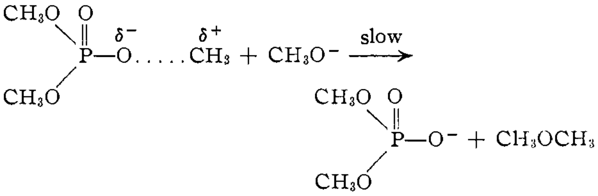
kcal. per mole may be attributed to the difference in mechanism involved. Since in solvolysis reactions the observed reaction order is not indicative of the mechanism, other considerations must be used to show the course of the reaction.[15] While a number of tests which may be used to differentiate between acyl–oxygen and alkyl–oxygen fission in the case of carboxylate esters are undoubtedly also applicable to phosphate esters, the nature of the reaction products in the present investigation together with the calculated entropies of activation provide evidence as to the mechanisms involved in reactions 6 and 9, respectively. The former reaction undoubtedly proceeds by an SN2 process involving nucleophilic attack on phosphorus by methoxide ion



The high lability of the aromatic group under basic conditions also has been observed by Hudson and Keay[16] who showed exclusive release of *p*-nitrophenol from ethyl *p*-nitrophenyl methylphosphonate in aqueous alkaline solution. The value obtained for the entropy of activation, $\Delta S^{\ddagger}$, −25.2 e.u., is in the range expected for a bimolecular mechanism proceeding through the usual constrained transition state.[17] The slower rate observed for (9), together with the formation of dimethyl ether indicates alkyl–oxygen cleavage rather than attack on phosphorus. In the carboxylic ester series, Bunnett, Robison and Pennington[18] have demonstrated that alkyl–oxygen cleavage took place when methyl benzoate was allowed to react in dry methanol with sodium methoxide to give benzoic acid and dimethyl ether, and have provided evidence that the latter reaction was one of those rare instances of carboxylate ester cleavage involving nucleophilic displacement at the alkyl carbon atom. While positive values for $\Delta S^{\ddagger}$ have been associated[19] with a unimolecular mechanism involving alkyl–oxygen cleavage, for example in the acid-catalyzed hydrolysis of *t*-butyl 2,4,6-trimethylbenzoate, the value of −6.0 e.u, for reaction 9 does not appear consistent with a mechanism involving the formation of a carbonium ion. This situation is particularly true since the species involved would be a methylcarbonium ion. On the other hand, a difference of 25 to 30 entropy units has been employed[17] as a criterion for differentiating between bimolecular and unimolecular processes in the rate-determining step. A possible mechanism for (9) which would be consistent with the kinetic data would involve partial dissociation of the trimethyl phosphate with the charge separation stabilized by a high degree of solvation



In the rate-determining step, methoxide ion cleaves the alkyl-oxygen bond to form dimethyl phosphoric acid and dimethyl ether



The kinetic data indicate that the latter step is bimolecular.

Reaction 10 follows the same route as (9) with the exception that it is slower by a factor of six or seven, which may be attributed to the lower nucleophilicity of the phenoxide as compared with the methoxide ion.[20]

By analogy with (6) and (9), the reaction of sodium phenoxide with dimethyl phenyl phosphate might be expected to proceed at a considerably faster rate than with trimethyl phosphate because of the favorable activation energy for elimination of aryl substituents in alkyl aryl phosphates by nucleophilic displacement on phosphorus. In the present instance, no chemical reaction would be evident. We have not attempted to study this possibility by the use of different aryl groups in the base and ester. The other possibility involving ester interchange by phenoxide attack on phosphorus is that illustrated by reaction 13, originally considered by us as less probable than (12). Route 13 would be expected to be slow inasmuch as sodium methoxide is a very strong base compared with sodium phenoxide. This expectation is supported by the fact that the ratio of the reaction rate constants k_{13}/k_{10} was only two whereas k_6/k_9 was 100 (the subscript here referring to the reaction involved). The decrease in value of the rate constants with time is evidence that the major reaction involved is probably an equilibrium

$$(CH_3O)_2(PhO)PO + PhONa \rightleftarrows (CH_3O)(PhO)_2PO + CH_3ONa$$

The presence of anisole among the reaction products may be attributed in part to some reaction *via* route 12 and in part to the formation of sodium methoxide (*via* the equilibrium reaction) which in turn would convert part of the dimethyl phenyl

---

(15) E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941); *Quart. Revs.* (*London*), **4**, 245 (1951).

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

(17) F. A. Long, J. G. Pritchard and F. E. Stafford, THIS JOURNAL, **79**, 2362 (1957).

(18) J. F. Bunnett, M. M. Robison and F. C. Pennington, *ibid.*, **72**, 2378 (1950).

(19) V. R. Stimson and E. J. Watson, *J. Chem. Soc.*, 2848 (1954).

(20) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956); see Table 2.

phosphate to trimethyl phosphate. The latter subsequently could react with phenoxide to form anisole. The measured rate constant is then the steady state value for these processes at any given time.

The extremely rapid rate of attack by sodium methoxide upon dimethyl phenyl phosphate explains the low yields of the latter in preparations involving the addition of aryl phosphorodichloridate to sodium methoxide solution.

The third method cited previously for the synthesis of mixed alkyl aryl phosphates, wherein both the alkoxide and the dichloridate are metered simultaneously into a reaction vessel at a rate such that neither reactant is in significant excess, gives excellent product yields. The reaction is extremely rapid and may be conducted at any temperature, including mild reflux temperatures. In the first experiments along these lines, phenolphthalein was employed as an internal indicator to facilitate control of the rate of addition of the reactants. Subsequent reactions, controlled potentiometrically, made it possible to increase the yields of crude product to 95–97%. In actual practice it was possible to hold the *p*H range by manual control of reactant feed rates to ±2 units. In the vicinity of *p*H 7, the indicated reading is sensitive to small changes in dichloridate or alkoxide concentration. Usually the reactants were added to a small volume of a liquid reservoir, inert solvent (*e.g.*, benzene or toluene), alcohol or phosphate ester from a previous run. With increasing quantity of product in the reaction vessel, *p*H control became much easier. Because of the very rapid rate of the major reaction 5, an excess of alkoxide is immediately detected by an increase in *p*H. The slower rate of the solvolysis reaction when dichloridate is in excess

$$ArOPOCl_2 + 2ROH \longrightarrow (RO)_2(ArO)PO + 2HCl \quad (14)$$

permits a slight build-up of acidic materials before a *p*H drop is indicated on the meter.

Although the potentiometry of the reaction calls for simultaneous addition of dichloridate and alkoxide at *p*H 5–7, side reactions 6 and 13 may take place as a result of trace local excesses of the alkoxide. By carrying out the process at an indicated *p*H of 2–4 and then adjusting to *p*H 4–6 before filtering sodium chloride and distilling off solvent alcohol, the extent of these side reactions was considerably reduced. Fractionation of the resulting product under reduced pressure gave the desired ester in high purity.

Equation 6 shows that sodium phenoxide and trimethyl phosphate are formed from the ester interchange reaction. The phenoxide reacts at a more rapid rate with the aryl phosphorodichloridate than with ester in (10) or (13)

$$\begin{tikzcd}
ArOPOCl_2 \arrow[r, "PhONa"] & (ArO)_2POCl \arrow[r, "PhONa"] \arrow[dr, "CH_3ONa"'] & (ArO)_3PO \\
 & & (CH_3O)(ArO)_2PO
\end{tikzcd}$$

As a result of these side reactions some di- or triaryl phosphates are obtained *via* the sodium alkoxide route. In the preparation of 4-chloro-3-methylphenyl dimethyl phosphate, for example, the increased aryl ratio was demonstrated in a product from which trimethyl phosphate had been removed. The analysis of the resulting crude ester was somewhat low in phosphorus and high in chlorine. *Anal.* Calcd. for $C_9H_{12}O_4ClP$: Cl, 14.15; P, 12.39. Found: Cl, 14.6; P, 12.0. By carrying out the alkoxide reaction at a lower *p*H, the extent of these side reactions was reduced somewhat.

In general, the simultaneous addition technique is most useful for the synthesis of trialkyl phosphates and of mixed alkyl aryl phosphates where contact with aqueous media is to be avoided because of hydrolytic instability. The desired degree of purity of the dialkyl aryl ester is achieved by conventional vacuum distillation of the crude product.

Acknowledgments.—The authors wish to express their appreciation to Dr. M. E. Griffing and Miss Shirley Trapp for assistance with the infrared studies and to Prof. H. C. Brown and Dr. E. G. DeWitt for helpful discussions.

Experimental

Syntheses of Dialkyl Aryl Phosphates from Secondary Phosphite Esters.—Dialkyl aryl phosphates were prepared by treating a 1:1 solution of secondary alkyl phosphites in carbon tetrachloride or diethyl ether at 0–5° with *ca.* 0.5–1 g. of chlorine gas in excess of the stoichiometric amount. After removing volatiles at 25–40° under atmospheric pressure, the crude chloridate was treated directly with a solution of the phenol in 25% aqueous sodium hydroxide. An equimolar amount of the dialkyl phosphorochloridate was added dropwise to the alkaline solution over 0.5–1 hr. at 10–15°, followed by an additional hour of stirring at 20–30°.

An excess of phenol was avoided because of difficulties encountered in removal of the excess reactant, particularly in the case of phenoxides having low water solubility. After benzene dilution, the more soluble phenoxides were removed by extraction with cold 10% sodium hydroxide solution, followed by a water wash, drying and freeing of the solvent. In the case of *p*-(1,1,3,3-tetramethylbutyl)-phenol, however, the alkali phenoxide was only very slightly soluble in 10% aqueous sodium hydroxide. In this case, the chloridate was added to the alkali phenoxide slurry. Here, and in the case of the *p*-chlorophenyl analog, the unreacted phenol was removed by a series of successive washes at 25° with 10% alkali. After each extraction, the aqueous layer was acidified with concentrated hydrochloric acid. When a separate oily layer (free phenol) was no longer precipitated, no more free phenol could be detected spectrophotometrically in the product. Final purification was achieved by vacuum distillation.

Phosphorylation.—A typical phosphorylation was carried out as follows: A mixture of 1.33 g. (0.01 mole) of aluminum chloride in 206.6 g. (2 moles) of phosphoryl chloride was heated to 90–95° and 108 g. (1 mole) of *m*-cresol was added dropwise with stirring over a period of 25 minutes. The temperature was allowed to rise rapidly to 100–105°. Phosphoryl chloride carried past the reflux condenser by the evolution of hydrogen chloride was collected in two cold traps (−70°). The hydrogen chloride was absorbed in water and titrated with standard sodium hydroxide to determine the end of the reaction. Then excess phosphoryl chloride was distilled off at 35–60°, initially at 100 mm. and finally at 1 mm. The dichloridate and monochloridate were fractionated at 1 mm. in a 12-inch Vigreux column. The data from a run with *m*-cresol are given in Table IV.

Determination of Active Chlorine in Solvent-free Phosphorochloridates.—Titration for active chlorine in a mixture of aryl mono- and dichloridates freed of phosphoryl chloride was carried out by means of the following procedure. A 10.15-g. sample of the mixed chloridates was added to 100 ml. of methanol and rapidly titrated at 25° with 15.45 ml. of 4.11 *N* sodium methoxide solution to *p*H 7, using a blue point Beckman glass electrode. A second sample (11.05 g.) was added to 100 ml. of methanol and maintained at 30° for 2.5 hours. It was then potentiometrically titrated

TABLE IV

FRACTIONATION OF PHOSPHORYLATION PRODUCT FROM THE REACTION OF *m*-CRESOL WITH PHOSPHORYL CHLORIDE

	Distillation data									
Cut	B.p. °C.	Mm.	Compn. of distillate	Wt. G.	Wt. Moles	Convers. (%, on cresol)	Material balance P	Material balance Cresol	Recovery, % P	Recovery, % Cresol
1	55–58	105	$POCl_3$	256	1.68		1.68			
2	90–97	1.0	$ArOPOCl_2$[a]	413	1.83	91.5	1.83	1.83		
3	160–164	1.0	$(ArO)_2POCl$	19.5	0.066	3.3	0.066	0.13		
Traps			$POCl_3$	45.0	.294		.294			
Pot residue			$(ArO)_3PO$	7.5	.02	1.0	.02	0.06		
						Total	3.89	2.02	97.2	101

[a] Ar = *m*-tolyl.

to *p*H 7.5–8 (phenolphthalein end-point) using 72.25 ml. of 0.959 *N* NaOH. The close agreement between these titrations, 0.626 and 0.627 equivalent of base, respectively, indicates either procedure to be satisfactory for the determination of total active halogen.

Reaction of Dimethyl Phenyl Phosphate with Sodium Methoxide.—For the determination of the reaction path (equations 6, 7 or 8) taken by dimethyl phenyl phosphate and sodium methoxide, 5.05 g. (0.025 mole) of the former was mixed with 6.25 ml. of 4 *N* sodium methoxide (0.025 mole) and maintained at 18° for 9 minutes. The solution then was poured rapidly into 100 ml. of water to quench the reaction. Four ml. of carbon disulfide was added to the solution and the resulting mixture subjected to distilling at 25° under reduced pressure (100 mm.) with the volatiles condensed in a train of three cold traps at −70°. When the carbon disulfide had come off, another 4 ml. of disulfide was added to the quench water and the process repeated. The volatiles were washed from the traps with fresh carbon disulfide and made up to 25 ml. No dimethyl ether was detected by infrared analysis. The limit of detection of this ether had been established as 0.01 g./25 ml. of disulfide. Hence, if any dimethyl ether had been present, it would have been less than 0.00022 mole, or approx. 1% of the dimethyl ether which would have resulted had the reaction gone exclusively *via* equation 8. A blank run, carried out with a dimethyl ether solution in methanol, corresponding with the quantities involved in the above experiment and involving a quench and solvent-removal, indicated better than 80% recovery of dimethyl ether by this procedure.

The aqueous residue, after drying, was saturated with sodium chloride and extracted with three 50-ml. portions of carbon disulfide. No anisole was detected, indicating reaction 7 had not taken place. Trimethyl phosphate was found in this extract but no dimethyl phenyl phosphate, indicating that the ester interchange had gone to completion. The aqueous residue from the disulfide extraction was acidified, extracted again with disulfide and the latter extract examined spectrophotometrically. Phenol was found in confirmation of route 6. From a material balance of the various extracts, trimethyl phosphate and phenol were shown to be present in approximately equimolar amounts.

Reaction of Dimethyl Phenyl Phosphate with Sodium Phenoxide.—This run was carried out by mixing 5.05 g. (0.025 mole) of dimethyl phenyl phosphate with 19.25 ml. of 1.30 *N* sodium phenoxide in methanolic solution. The latter had been prepared by adding sodium methoxide to an excess of phenol. Since the resulting solution was 1.5 molar in phenol (*i.e.*, 0.2 molar excess of free phenol), the possibility for the presence of sodium methoxide was minimized. After 200 hours at 43°, the reaction solution was quenched in 100 ml. of ice-water containing 4 ml. of 0.992 *N* sodium hydroxide in order to convert the free phenol to its sodium salt and thus prevent it from being extracted. The quench solution was subjected to five 40-ml. extractions with carbon disulfide and the extracts were combined for infrared analysis. Anisole (0.016 mole) was detected, but no diphenyl ether. This result was taken as evidence for equation 12 since under the conditions of the extraction diphenyl ether should have been detected had the reaction proceeded *via* route 11.

Kinetic Studies: Dimethyl Phenyl Phosphate and Sodium Methoxide.—The dimethyl phenyl phosphate used was prepared by the reaction of aqueous sodium phenoxide with dimethyl phosphorochloridate, purified by caustic extraction to remove phenol and redistilled twice under vacuum in a packed column. A heart cut boiling at a constant value, 115° at 2.2 mm. (n^{20}_D 1.4887, d^{20}_4 1.2283), was selected. Infrared analysis indicated the phenol content to be less than 0.02% if any. *Anal.* Calcd. for $C_8H_{11}O_4P$: C, 47.6; H, 5.49; P, 15.4. Found: C, 47.9; H, 5.67; P, 15.6. A standard solution of this material, 1.000 molar, was prepared by weighing and dissolving in methanol which had been distilled from metallic sodium and kept over anhydrous sodium sulfate in tightly stoppered bottles. Sodium methoxide, 1.424 molar, was prepared by diluting from a 4 molar stock solution.

The kinetic studies were carried out by mixing 50.0-ml. of the reagents and assuming no volume change due to mixing. A correction, however, was applied for temperature. Since mixing was exothermic, the mixing at the two higher test temperatures, 10.04° and 19.01°, was carried out in erlenmeyer flasks cooled in ice-water. Approximately 3–4 minutes was required in each case to bring the flask and contents to the desired temperature in a thermostated bath held at ±0.05°. The zero sample usually was taken at ten minutes from the time of mixing. The sodium methoxide concentration in this sample was determined from the *p*H titration curve as described below. From this value and the original normality, the number of moles of alkali consumed during mixing and equilibration was calculated. The ester was considered to have decreased in concentration by like amount. In this way, the zero concentrations were calculated.

One of the problems encountered was to quench a sample of the reaction solution effectively at various time intervals. Ten-ml. samples were added to 100 ml. of distilled water which had been cooled to 0° in an ice-bath and then potentiometrically titrated with 1.012 *N* HCl in a Dow precision dual recordomatic titrometer. The total time from quenching until completion of the titration was less than three minutes. Manual titrations did not show a sharp break in the *p*H curve at *ca.* *p*H 11–12 unless less quench water was used. Unfortunately because of this factor and the longer time, hydrolysis of the ester by sodium hydroxide took place, giving erroneous results. Two titration breaks were observed, one at *p*H 11.6 (Beckman type E No. 4990-75 glass electrode) representing sodium methoxide concentration (actually sodium hydroxide in the quench solution), another at *p*H 6 representing total titratable alkali; the difference between the two inflections was equivalent to sodium phenoxide concentration. The rate of disappearance of methoxide was measured by following the decrease in titer at the *p*H 11.6 break. The value of the *p*H 6 break was used for a twofold purpose, to check against sampling errors, and to permit correction for the reaction temperature volume change. The data obtained are recorded in Table III.

Kinetic Studies with Trimethyl Phosphate and Sodium Methoxide.—The trimethyl phosphate employed was obtained from Monsanto Chemical Co., dried over anhydrous sodium sulfate and purified by distillation *in vacuo*. A constant boiling heart cut (b. 110° at 50 mm.) was used. *Anal.* Calcd. for $C_3H_9O_4P$: C, 26.7; H, 6.5; P, 22.1. Found: C, 26.8; H, 6.5; P, 22.0; n^{20}_D 1.3957 (lit. value 1.3963). The concentration used for the kinetic studies was 1.00 molar (in methanol).

Three runs were carried out (see Table III) at 25.00, 33.81 and 42.70°. Equal volumes of standard trimethyl phosphate and sodium methoxide were used. Twenty-five ml. samples were removed at various times, quenched in 100 ml. of water and titrated with standard acid to the phenolphthalein end-point. As in the corresponding runs with dimethyl phenyl phosphate, a plot of 2.303 log *k* against $1/T$ (°K.) gave an excellent straight line in accordance with second-order kinetics.

Kinetic Studies: Reactions with Sodium Phenoxide.—The sodium phenoxide reagent had been prepared from a concentrated solution of C.P. phenol in dry methanol by the addition of a 4 *N* sodium methoxide solution. Upon further methanol dilution the resulting solution was 1.30 molar in sodium phenoxide and 1.50 molar in total phenol, that is, with 0.20 mole free phenol per liter.

In a run with dimethyl phenyl phosphate, 50 ml. of the phenoxide solution and an equal volume of the ester (1.00 molar) were allowed to react at 42.24°. Ten-ml. samples were quenched at intervals in 100 ml. of distilled water and titrated with 1.012 *N* hydrochloric acid to the methyl orange end-point with the results given in Table V.

TABLE V

KINETIC DATA FOR THE REACTION OF SODIUM PHENOXIDE WITH DIMETHYL PHENYL PHOSPHATE

Accumulated time, min.	CH_3ONa, (mole/l.)[a]	Ester, (mole/l.)[a]	Reacted, %	10^5k (calcd.),[b] l. mole^{-1} sec.$^{-1}$
0	0.643	0.4936	0	..
40	.629		2.2	1.89
159	.597		7.2	1.66
279	.579		10.0	1.36
379	.567		11.9	1.22
572	.538		16.4	1.19

[a] Zero time taken after 10 minutes equilibration with corrections for change in reactant concentration as described in text. [b] Calcd. from equation for second-order kinetics.

A run with trimethyl phosphate and sodium phenoxide, at 43.50°, on the other hand, yielded good second-order data (Table III).

Preparation of Dimethyl *m*-Tolyl Phosphate.—To employ the simultaneous addition procedure under controlled *p*H conditions, the reaction vessel was provided with openings to accommodate a glass and calomel electrode pair connected to a Beckman model H2 *p*H meter. The electrodes were immersed in 30–50 ml. of solvent, usually alcohol. *m*-Tolyl phosphorodichloridate (225 g., 1.0 mole) was treated by adding simultaneously in dropwise fashion with 575 ml. of sodium methoxide solution (containing 48.2 g. sodium) over 40 minutes while maintaining the reaction solution at 62° and at *p*H 6 ± 2. After filtering sodium chloride, the methanol was removed at aspirator pressure (50°) and the product washed with two 100-ml. quantities of 5% sodium hydroxide solution and two 100-ml. volumes of water. The resulting dimethyl *m*-tolyl phosphate, dried over sodium sulfate, was a pale yellow oil weighing 203 g. (94% crude yield). *Anal.* Calcd. for $C_9H_{13}O_4P$: C, 50.0; H, 6.0; P, 14.3. Found: C, 49.6; H, 5.90; P, 14.6.

Although high yields have been obtained with fairly concentrated solutions of alkoxide, for ease of feed control a concentration should be selected which is fluid rather than gel-like. Reactions with sodium methoxide have been carried out at concentrations equivalent to 10–13% sodium (*i.e.*, g. of sodium per 100 g. of sodium + methanol). Attempts to reduce the alcohol volume further resulted in viscous solutions of high freezing point. Furthermore, above 14% sodium, the formation of methoxide was hindered even under reflux because of coating of the sodium surface by the product.

Preparation of 4-Chloro-3-methylphenyl Dimethyl Phosphate.—To reduce undesirable side reactions caused by small local excesses of sodium alkoxide, 4-chloro-3-methylphenyl dimethyl phosphate was prepared by simultaneously feeding 0.5 mole (130 g.) of the corresponding dichloridate and 246 ml. of 4.07 *N* sodium methoxide while maintaining the *p*H range at 1–3 and holding the temperature at gentle reflux (55–69°) by external cooling. The *p*H was adjusted to 4 before filtering sodium chloride and the methanol was evolved at 40–50° under aspirator pressure. The product was washed once with 125 ml. of 7.5% sodium carbonate, twice with 50-ml. quantities of 1% sodium chloride, and then dried by vacuum distilling at 1 mm. (50°). *Anal.* Calcd. for $C_9H_{12}O_4ClP$: P, 12.39; Cl, 14.15. Found: P, 12.0; Cl, 14.6. The weight of product, 119.9 g., corresponds to a 95.7% crude yield. Distillation yielded 108 g. of pure 4-chloro-3-methylphenyl dimethyl phosphate, b.p. 131° (0.75 mm.). *Anal.* Found: P, 12.3; Cl, 14.0.

DETROIT 20, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, ETHYL CORPORATION]

The Synthesis of Alkyl Aryl Phosphates from Aryl Phosphorochloridates. II. The Solvolysis Route[1,2]

BY HAROLD D. ORLOFF, CALVIN J. WORREL AND FRANCIS X. MARKLEY

RECEIVED JULY 30, 1957

The solvolytic reaction of phosphorochloridates with alcohols may be employed under controlled conditions for the preparation of phosphate esters in high yield. The major drawback to this procedure is cleavage of the alkyl–oxygen bond of the ester as a result of a bimolecular displacement by hydrogen chloride which is a by-product of the reaction. In the presence of excess alcohol, the cleavage reaction is slowed down as a result of oxonium salt formation. Procedures for following the rates of cleavage and of esterification have been developed to give yield data which are in good agreement with those obtained by physical isolation of the reaction product.

Although a number of phosphate esters have been synthesized in good yield from the corresponding chloridates by solvolysis in alcoholic solution[3,4], an understanding of the reaction is restricted largely to alkyl chloridates and to some of the side reactions of the alkyl esters derived from them. From kinetic[5] and isotopic[6] studies of the solvolyses of dialkyl phosphorochloridates, reactions with nucleophilic reagents have been found to proceed by a bimolecular mechanism identical with that of S_N2 reactions of analogous carbon compounds. No evidence has been obtained for an intermediate complex which slowly decomposes into the products.

The methanolysis of aryl phosphorodichloridates proceeds in two stages with liberation of hydrogen chloride

$$ArOPOCl_2 + CH_3OH \longrightarrow (CH_3O)(ArO)POCl + HCl \quad (1)$$

$$(CH_3O)(ArO)POCl + CH_3OH \longrightarrow (CH_3O)_2(ArO)PO + HCl \quad (2)$$

which in turn attacks the neutral ester product in a

---

[1] Part I of this series, H. D. Orloff, C. J. Worrel and F. X. Markley, THIS JOURNAL, **80**, 727 (1958).

[2] Presented before the Division of Organic Chemistry, 131st Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957.

[3] G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 211.

[4] F. Nicolai, C. Schoenburg and G. V. der Bruck, U. S. Patent 1,869,768, Aug. 2, 1932.

[5] I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 502, 508, 516 (1953).

[6] I. Dostrovsky and M. Halmann, *ibid.*, 1004 (1956).