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 SN2 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

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[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).

cleavage reaction from which a phosphoric acid and an alkyl halide are obtained

$$(CH_3O)_2(ArO)PO + HCl \longrightarrow (CH_3O)(ArO)POOH + CH_3Cl \quad (3)$$

Whereas in alkaline reactions hydrolysis of phosphate and phosphonate esters proceeds predominantly by breaking of the P–O aryl bond,[7] acid-catalyzed hydrolysis involves alkyl–oxygen fission.[8] With alkyl aryl phosphates, the products of cleavage are the mixed alkyl aryl hydrogen phosphate, (RO)(ArO)POOH, and the corresponding alkyl halide. Alkaline rather than acid hydrolysis, on the other hand, would be employed to prepare the dialkyl acid, $(RO)_2POOH$, from the dialkyl aryl phosphate, $(RO)_2(ArO)PO$. This observation is in agreement with information reported[7] on the hydrolysis of 2-dichloroethyl diphenyl phosphate with alcoholic alkali in which the phenyl group was lost at a faster rate than the alkyl group.

Cleavage Reaction.—Inasmuch as hydrogen chloride is a by-product in the preparation of dimethyl aryl phosphates by the methanolysis of the corresponding phosphorodichloridate, the rate of the cleavage reaction 3 exerts a profound influence upon the yield of the neutral ester. From a better understanding of the course of the cleavage mechanism it has been possible to minimize its effects upon the synthesis of the mixed ester and thereby obtain higher yields of the latter.

The rate of the cleavage reaction was established by following the disappearance of chloride ion in mixtures of dimethyl aryl phosphates and dry hydrogen chloride, in the absence of solvent, over the temperature range 20–40° (Table I). This approach was utilized in order to approach conditions encountered in some of the synthetic work and to eliminate complications from solvent interactions with the hydrogen chloride or ester. The data were in agreement with second-order kinetics. In the case of dimethyl *m*-tolyl phosphate, for example, a plot of log k against $1/T$ (°K.) gave a straight line from the slope of which the Arrhenius activation energy and frequency factor were calculated: E, 16.0 kcal./mole; log A, 8.78. The entropy of activation, $\Delta S^{\ddagger}$, was calculated as -28.4 e.u.

TABLE I

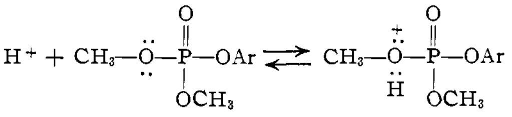
CLEAVAGE REACTION OF DIMETHYL ARYL PHOSPHATES WITH DRY HYDROGEN CHLORIDE IN THE ABSENCE OF SOLVENT

Run	Aryl group	Temp., °C.	10^5k, l. mole^{-1} sec.$^{-1}$
1	*m*-Tolyl	20.0	1.22
2	*m*-Tolyl	30.0	3.02
3	*m*-Tolyl	40.0	7.04
4	*p*-Tolyl	30.0	3.0
5	4-Chloro-3-methylphenyl	30.0	1.5

A comparable and well-known reaction that involves rupture of an alkyl–oxygen bond is the formation of an alkyl halide from an alcohol.[9] The reactions of various alcohols with hydrogen chloride and hydrogen bromide have activation energies of 26–31 kcal. per mole. By contrast, reactions of carboxylic acids with alcohols, involving acyl–oxygen fission, have values of 10–15 kcal. per mole which are comparable with the activation energy of 16 kcal. per mole for the cleavage of dimethyl *m*-tolyl phosphate. Since in the latter case, the nature of the products formed is adequate evidence for alkyl–oxygen fission, the lower activation energy may be explained on the basis of electron-withdrawing effects in the phosphate ester molecule. These may be ascribed to the electromeric effect $\overset{\curvearrowright}{P{=}O}$ or to electron withdrawal by the aromatic group or both.

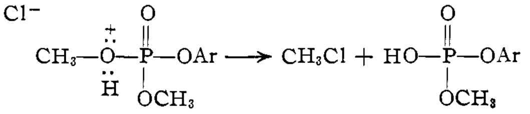
Inasmuch as the major object of the present investigation was a study of synthetic methods by the solvolysis route, the effect of substituents in the aryl group upon the rate of cleavage was restricted to the *p*-tolyl, *m*-tolyl and 4-chloro-3-methylphenyl isomers. Essentially no difference in cleavage rate was observed with the *p*-tolyl (run 4) as compared with the *m*-tolyl ester (run 2). Introduction of a *p*-chloro substituent into the *m*-tolyl derivative (run 5), on the other hand, decreased the reaction rate by a factor of two.

That the reaction is bimolecular is evident on the basis of the following information: (1) the second-order kinetic data; (2) the magnitude of the entropy of activation, $\Delta S^{\ddagger}$, -28.4 e.u.[1]; and (3) separation of a methylcarbonium ion *via* unimolecular ionization would be energetically difficult. A two-step mechanism may be considered for the cleavage reaction. The first step may be reversible rapid protonation to form the conjugate acid



$$H^+ + CH_3{-}\ddot{\underset{\cdot\cdot}{O}}{-}\underset{\substack{|\\ OCH_3}}{\overset{\substack{O\\ \|}}{P}}{-}OAr \rightleftharpoons CH_3{-}\underset{\substack{\cdot\cdot\\ H}}{\overset{+}{\ddot{O}}}{-}\underset{\substack{|\\ OCH_3}}{\overset{\substack{O\\ \|}}{P}}{-}OAr \quad (4)$$

The latter then would undergo irreversible nucleophilic (S_N2) displacement of the methyl group by chloride ion



$$\overset{Cl^-}{CH_3}{-}\underset{\substack{\cdot\cdot\\ H}}{\overset{+}{\ddot{O}}}{-}\underset{\substack{|\\ OCH_3}}{\overset{\substack{O\\ \|}}{P}}{-}OAr \longrightarrow CH_3Cl + HO{-}\underset{\substack{|\\ OCH_3}}{\overset{\substack{O\\ \|}}{P}}{-}OAr \quad (5)$$

Since the electron-withdrawing property of the *p*-chloro substituent in dimethyl 4-chloro-3-methylphenyl phosphate decreases the basicity of the alkyl–oxygen atom, its effect would be to reduce protonation. The fact that cleavage of this ester is slower than that of the *m*-tolyl analog suggests that the protonation step 4 is a requirement of the reaction and favors the cleavage reaction in step 5.

The importance of protonation has been established from an alternate approach. In the presence of methanol, cleavage rates lower than those obtained in the absence of solvent have been observed. Fitting ester and hydrogen chloride concentrations to the expression for second-order reactions gave, for an individual run, reaction rate constants which indicated second-order kinetics. However, as the methanol:hydrogen chloride ratio was altered, different values for the rate constant

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[7] R. Hazard, P. Chabrier, A. Carayon-Gentil and Y. Fievet, *Compt. rend.*, **240**, 986 (1955).

[8] E. Blumenthal and J. B. M. Herbert, *Trans. Faraday Soc.*, **41**, 611 (1945); P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, K. G. Oldham, B. L. Silver and C. A. Vernon, *Chemistry & Industry*, 760 (1955); R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

[9] G. M. Bennett and F. M. Reynolds, *ibid.*, 131 (1935); C. N. Hinshelwood, *ibid.*, 599 (1935).

were obtained; the greater the excess of alcohol, the smaller the value obtained for k (Table II). Four runs were carried out with an identical quantity of dimethyl m-tolyl phosphate and methanol in each case (40.0 and 6.11 g., respectively; mole ratio, 1:1.03). Varying amounts of dry hydrogen chloride were introduced, and the rate of disappearance of chloride ion was measured.

TABLE II

EFFECT OF METHANOL:HYDROGEN CHLORIDE MOLE RATIO ON CLEAVAGE REACTION RATE CONSTANT OF DIMETHYL m-TOLYL PHOSPHATE AT 30.0°

Reactants charged, moles/liter			Mole ratio methanol : HCl	10^4k, l. mole^{-1} min.$^{-1}$
Ester	Methanol	HCl		
3.66	None	1.66	0	18.1
2.80	2.89	4.79	0.60	12.6
2.96	3.05	3.80	0.80	10.4
3.14	3.24	2.68	1.21	8.9
3.26	3.36	1.98	1.69	8.1

From an inspection of a plot (Fig. 1) of the data, it appears that an extrapolation of the slopes at low and high methanol:hydrogen chloride mole ratios gives lines which intersect fairly close to a 1:1 ratio. These results indicate that in the solvolysis of chloridates by alcohols, at least one mole of excess alcohol should be present per mole of hydrogen chloride formed to reduce product loss by cleavage.

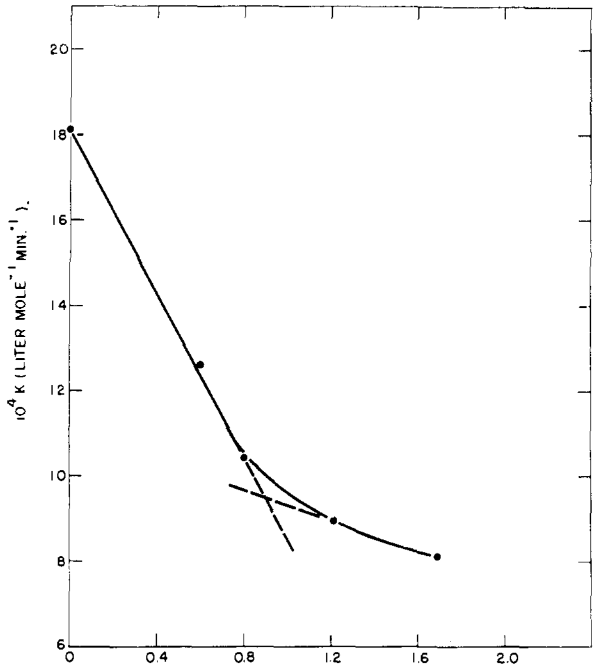

Fig. 1.—Effect of mole ratio of methanol to hydrogen chloride on cleavage rate constant.

This protective effect of the alcohol may be explained in terms of solvation or hydrogen bonding[10,11] to form an oxonium salt $CH_3{:}\underset{H}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}}{:}HCl$ which may interfere with the cleavage reaction in two ways: 1. Protonation of the C–O–P oxygen is reduced, thereby decreasing the concentration of the activated complex. 2. The oxonium salt is less effective than hydrogen chloride in consummating the alkyl–oxygen fission from the protonated complex.

The over-all rate would depend on the ratio of the two species, HCl and $CH_3{:}\underset{H}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}}{:}HCl$ (which in turn is dependent upon the alcohol:hydrogen chloride ratio and the equilibrium constant for the oxonium salt formation) and on their relative reactivity.

The protective effect of methanol suggests that due to reduced cleavage higher yields of phosphate ester should be realized in runs employing excess methanol. A consideration of the data for various intermediates indicates that at least 100% excess methanol, or at least two moles of alcohol per equivalent (35.46 g.) of replaceable chlorine (P–Cl) in the chloridate are required, one mole for replacement of the halogen, the other to solvate the hydrogen chloride formed. In line with these observations it was noted that addition of the dichloridate to methanol gave larger yields than with the reverse order of addition.

The products of the cleavage reaction have been examined by infrared spectrophotometry in an attempt to ascertain whether aryl–oxygen fission took place; no evidence for the resultant aryl chloride (phenyl, m-tolyl or 4-chloro-3-methylphenyl) could be found. Isolation of the acid prepared from cleavage reactions carried out at 25–40° indicated it to be essentially pure monobasic methyl aryl hydrogen phosphate, $(CH_3O)(ArO)POOH$. However, heating of the hydrogen chloride:dimethyl aryl phosphate ester solution to 60–100° resulted in the formation of some dibasic acid as well. Since these represent unusual conditions, the nature of the other products was not investigated.

The Course of the Methanolysis Reaction.—In the investigation of the effect of reaction variables upon the yield of phosphate ester, a simple analytical approach was preferred to a strictly synthetic route which involved physical separation of the ester, particularly in the presence of excess methanol which complicated the separation process. A procedure has been established which makes it possible to follow both the solvolytic replacement of chlorine in P–Cl bonds by alcohols and the extent of the competing cleavage reaction. By plotting the curves for each of these effects, the conditions for maximum yield of ester may be established. At this point, routine organic chemical procedures may be considered from the standpoint of product recovery.

It will be recalled from equation 2 that in dry alcohol one equivalent of acid (hydrogen chloride) is formed for each reactive chlorine bonded to phosphorus (*i.e.*, P–Cl). For each mole of hydrogen chloride lost by cleavage, an equivalent quantity of phosphorus acid, herein abbreviated >POOH, will be formed (equation 3); the sum of HCl + >POOH is independent of the extent of cleavage. In an aqueous medium, on the other hand, two

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(10) E. Grunwald and S. Winstein, THIS JOURNAL, **69**, 2051 (1947).

(11) Hydrogen bonding with dioxane in the solvolysis by phenols of benzyl phosphates has been noted by G. W. Kenner and J. Mather, *J. Chem. Soc.*, 3524 (1956).

equivalents of acid are formed for each reactive chlorine

$$(CH_3O)(ArO)POCl + H_2O \longrightarrow (CH_3O)(ArO)POOH + HCl \quad (6)$$

Consequently titration of the hydrolysis product from (6) should give twice the consumption of standard alkali required for (2).[12] It is obvious then that the difference in equivalents of base required for reactions 6 and 2 is a direct measure of the equivalents of replaceable chlorine (P–Cl) remaining at any stage during the course of the solvolysis. This relationship is not affected by the presence of the cleavage acid, $(CH_3O)(ArO)POOH$, under the conditions investigated.

The solvolyses of phosphorochloridates and dichloridates have been followed in runs carried out at 0–35° with 50–300% excess methanol, *i.e.*, 0.5–3.0 moles excess methanol per equivalent of P–Cl. At these temperatures no hydrogen chloride or other components were lost from the solution. The procedure involved adding two weighed aliquots of the reaction solution, in one case to dry methanol, in the other to a solution of water in *p*-dioxane or other suitable medium, for example, acetone–water. After 4–6 hours, the solvolyzed products were diluted with distilled water and titrated with standard alkali to the phenolphthalein end-point. The use of the latter indicator has given values about 0.2% higher than were obtained at the potentiometric end-point (*ca.* *p*H 7.5 in methanol–water).

Determining the P–Cl content of the reaction solution as a function of time provided a simple means of following the esterification (*i.e.*, solvolysis) reaction. The value so obtained was not the theoretical yield because at this stage the extent of the cleavage reaction had not yet been taken into account.

The nature of the interpretative treatment involved may be illustrated with a hypothetical example. Consider the solvolysis of one mole of a phosphorochloridate from which two samples are removed after 85% solvolysis and during which 10% cleavage has taken place. One sample, treated with excess dry methanol, as described above, and then titrated with base, would indicate 1.00 equivalent of acid. The other, reacting in water–dioxane, would require 1.15 equivalents of base; subsequent titration of the latter solution for chloride ion by the Volhard method should indicate 0.90 equivalent of chloride ion. The distribution of products may be summarized as indicated in Table III.

TABLE III

DISTRIBUTION OF ACIDIC PRODUCTS FROM HYDROLYSIS OF SOLVOLYSIS MIXTURE IN AQUEOUS DIOXANE

Component	Concentration at time of sampling, equivalent	Acid formed in water-dioxane (equivalent)
HCl	0.75	0.75
>POOH	.10	0.10
>P-Cl	.15	0.15 (>POOH) + 0.15 (HCl)
Total	1.00	1.15

The amount of cleavage acid, >POOH, therefore is equal to: 1, Total initial replaceable chlorine (P–Cl) minus the Volhard chloride ion content of the sample hydrolyzed in water–dioxane, calculated on the basis of the same weight of chloridate; or 2, total acid by aqueous hydrolysis minus chloride ion in the same sample and minus unreacted P–Cl.

The equivalents of cleavage acid, >POOH, may be expressed as a percentage of the initial equivalents of replaceable chlorine.

With the development of this technique it was now possible to determine small differences in yield as the result of a change in reaction conditions with greater precision than when a lengthy extraction of the reaction product was carried out. For example, in one series, to show the effect of order of mixing of reactants, 0.5 mole of distilled 4-chloro-3-methylphenyl phosphorodichloridate (containing 1.00 equivalent of P–Cl) was added to 100% excess (2.0 moles) methanol at 30° over a 50-minute period (run 1) while in the second case (run 2) the order of addition was reversed. After a 25-minute cook period, samples were removed, quenched in methanol and water–dioxane, respectively, and titrated for acidity. From the data, the yields were calculated as shown in Table IV.

TABLE IV

CALCULATION OF PHOSPHATE YIELD ASSUMING NO CLEAVAGE

Run	Unreacted P-Cl, equiv.	P-Cl esterified, %	Max. yield (%) assuming[b] no cleavage
1	0.0427	95.73[a]	91.46
2	.0763	92.37	84.74

[a] 1.00–0.0427 = 0.9573 equivalent of P–Cl esterified. [b] 100 [1.00–2(0.0427)] = 91.46%.

Other results obtained in these laboratories indicate that the first chlorine atom of a dichloridate is solvolyzed more rapidly than the second. Thus, in the examples cited, where over 90% of the P–Cl bonds have been converted to $P-OCH_3$ groups, it is reasonable to expect that the remaining chloridate is a monochloridate rather than a mixture of neutral ester and dichloridate. Hence, 90% esterification of the P–Cl bonds corresponds to an 80% yield of ester (exclusive of hydrogen chloride cleavage) if the reaction were quenched at this point. This explains why the data in column 4 are lower than those in column 3. With dichloridates, therefore, a high percentage of esterification has an important bearing on product yield. For monochloridates, on the other hand, 90% solvolysis is equivalent to a 90% yield.

The rate of methanolysis was moderately rapid at 20°; approximately one hour was required for completion of the reaction when the mole ratio of methanol to *m*-tolyl phosphorodichloridate was 4:1 (Table V).

By carrying out the solvolysis under reduced pressure in the presence of 100% excess alcohol, it was possible to increase the rate of solvolysis to a minor extent. This may be attributed to removal of some of the hydrogen chloride, thereby reducing

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[12] At high temperatures (*e.g.*, 60–100°) a small amount of dibasic acid may be obtained. However, under normal conditions for the solvolysis of alkyl aryl phosphates (0–45°) the quantity of dibasic acid is less than 1% and may be differentiated potentiometrically if desired.

TABLE V

RATE OF METHANOLYSIS OF *m*-TOLYL PHOSPHORODICHLORIDATE AT 20° WITH A 4:1 MOLE RATIO OF METHANOL: DICHLORIDATE

Time, min.	Dichloridate, mole × 10^{-3}	1.0 *N* NaOH, ml.	HCl evolved (% of theory)
19	5.75	9.2	81
40	5.49	9.5	88
48	5.60	10.5	94
60	5.20	10.0	99
77	5.27	10.2	101

the concentration of the methanol-hydrogen chloride complex and increasing the availability of free methanol. Table VI compares the extent of solvolysis of 4-chloro-3-methylphenylphosphorodichloridate under atmospheric and reduced pressure conditions.

TABLE VI

EFFECT OF PRESSURE ON THE EXTENT OF SOLVOLYSIS

Run	Temp., °C.	Pressure, mm.	HCl free, mole	Unreacted P–Cl, equiv.
1[a]	30	760	0	0.0763
2[b]	30	760	0	.0427
3[c]	28	150	0.415	.026
4[c]	34	100	.639	.225
5[c]	34	200	.480	.022
6[c]	25	200	.255	.066

[a] Run 1. Addition of 2.0 moles (100% excess) of methanol to 0.5 mole of dichloridate over a 50-minute period, followed by a 25-minute "cook." [b] Run 2. Reverse addition, *i.e.*, dichloridate to methanol over 50 minutes, followed by a 25-minute "cook." [c] Run 3–6. Addition of methanol to dichloridate as in run 1. The entire reaction was maintained under reduced pressure and the hydrogen chloride evolved was absorbed in water containing phenolphthalein indicator; its rate of removal was followed by feeding 2 *N* sodium hydroxide solution such as to maintain a faint pink color. While the solvolysis was favored under reduced pressure conditions, controlling such a reaction was difficult with low boiling alcohols. Unless the temperature and pressure were carefully adjusted considerable alcohol was vaporized. At too low a temperature (run 6) insufficient hydrogen chloride came off to warrant the added effort. At too high a vacuum (run 4), considerable hydrogen chloride was removed but so also was methanol which had the effect of slowing down the reaction; in this instance, only 77.5% of the P-Cl bonds were esterified as compared with 97.8% in run 5. The conditions for the latter experiment represented a satisfactory balance of temperature and pressure. Under pressures of 100–200 mm. little or no external cooling was required to maintain the desired reaction temperature.

Experimental

Kinetics of the Cleavage Reaction.—The cleavage reaction was carried out by introducing dry hydrogen chloride gas through a 1-mm. capillary immersed in the desired amount (usually 0.2–0.5 mole) of redistilled dialkyl aryl phosphate. The mixture was kept at ice temperature until the desired weight gain was observed. Rapid introduction of the gas was achieved with a minimum of chemical reaction at this stage. The flask was then quickly warmed to the desired temperature (20–40°) and placed in a thermostated bath held within ±0.05°. Samples were withdrawn at intervals, quenched in 50 ml. of distilled water and titrated for chloride ion by the Volhard method. Total acid was determined on samples by titrating with standard alkali to the phenolphthalein end-point. Since one mole of strong acid, (RO)(ArO)POOH, was formed for every mole of hydrogen chloride which disappeared, the constancy of the acid titer served as a check on the weight of hydrogen chloride initially charged and as evidence that the latter was not lost from the solution during the course of the cleavage reaction at the concentrations and temperatures employed. In runs at the higher temperatures and with high hydrogen chloride concentrations, a 1–2% loss was encountered over a 3–4 hr. run. By averaging the hydrogen chloride concentration, a value within ±1% was determined for use in the rate calculations. The time at which the first sample was titrated was taken as the start of the reaction ($t = 0$). Since its chloride ion content was less than the concentration of hydrogen chloride charged due to cleavage during the warming up of the sample to the run temperature, a corresponding correction was made for the amount of phosphate ester cleaved at this point. To reduce errors in pipetting out measured volumes of the reaction solution, the latter was sampled by a gravimetric technique. The titration flask containing the 50 ml. of distilled water for quenching the reaction was weighed to 0.01 g. The sample (*ca.* 5–10 g.) was poured rapidly into the water, and the aqueous solution reweighed. Density corrections were applied to convert quantities used to a volume basis in order that the concentration of reagents could be expressed in terms of moles per liter.

The dimethyl aryl phosphates used for the kinetic studies reported in Table I were heart cuts obtained from fractionation of esters in a packed column at reduced pressure. The pertinent analytical data are given in Table VII.

TABLE VII

ANALYSES OF DIMETHYL ARYL PHOSPHATES USED IN KINETIC STUDIES

Aryl group	Analyses (wt. %) Calcd. P	Calcd. Cl	Found P	Found Cl	$n^{20}D$	d_4^{20}
m-Tolyl	14.4	..	14.5	..	1.4910	1.1907
p-Tolyl	14.4	..	14.2	..	1.4896	....
4-Chloro-3-methylphenyl	12.4	14.1	12.3	14.0	1.5074	....

Preparation of Methyl Aryl Hydrogen Phosphate.—One mole (251.5 g.) of 4-chloro-3-methylphenyl dimethyl phosphate was held at 40–45° while anhydrous hydrogen chloride was introduced until saturated (24 g. absorbed). After 2 hours, the solution was diluted with 300 ml. of benzene, neutralized with 4.10 *N* sodium methoxide solution and evaporated to dryness. The salt mixture (sodium chloride + sodium organophosphate) was dissolved in water, acidified and the phosphoric acid extracted with ether. After drying over sodium sulfate, the ether was removed and a 32% (76.0 g.) yield of 4-chloro-3-methylphenyl methyl hydrogen phosphate was recovered. A portion (35.0 g., 0.147 mole) of the oily acid was dissolved in 100 ml. of benzene, treated with 36.0 ml. of 4.10 *N* sodium methoxide, cooled to room temperature and filtered. After washing with benzene and drying, the white crystalline powder (37.0 g.) analyzed as the sodium salt of the monoaryl derivative.

Anal. Calcd. for $C_8H_9O_4ClNaP$: P, 11.99; Cl, 13.73; Na, 8.93. Found: P, 11.93; Cl, 13.86; Na, 9.07.

Determination of Reactive P-Cl.—The validity of the procedure for determining chlorine bonded to phosphorus during the course of solvolysis was checked by hydrolyzing both a pure chloridate and a pure dichloridate in dry alcohol and water-dioxane, respectively. Distilled bis-(4-chloro-3-methylphenyl) phosphorochloridate (8.71 g.) was added slowly with the aid of a hypodermic syringe to 100 ml. of dry methanol at 20–25° in a 250-ml. erlenmeyer flask and then set aside for four hours in a 30° bath. At the same time, a 2.18-g. aliquot of the chloridate was added to a solution of 20 ml. of water in 30 ml. of *p*-dioxane and left at 30° for a like period. The solutions were then diluted with 30 ml. of distilled water and titrated with standard base to the phenolphthalein end-point. From the respective titrations, 22.85 and 11.43 ml. of 0.959 *N* sodium hydroxide, the volumes of 1.00 *N* sodium hydroxide per 10.00-g. aliquot were calculated as 27.4 and 54.7 ml., respectively, or a ratio of 1:2 (calcd. 27.4 and 54.7 ml., respectively). Similarly, 4-chloro-3-methylphenylphosphorodichloridate gave results in good agreement with calculated values.

The Rate of Methanolysis of *m*-Tolyl Phosphorodichloridate.—The data reported in Table V were determined by a relatively simple technique. Small quantities (1.0–1.5 g.) of the dichloridate were weighed into thin-walled test-tubes, and 100% excess dry methanol (4:1 mole ratio) was added as quickly as possible, while maintaining the desired reaction temperature by external cooling. The samples then

TABLE VIII

DETERMINATION OF PERCENTAGE P–Cl ESTERIFIED

Time, min.	Sample wt., g. Water–dioxane	Sample wt., g. Methanol	Ml. 0.995 *N* NaOH Water–dioxane	Ml. 0.995 *N* NaOH Methanol	Diff., ml. NaOH per 208.5 g.[a]	Equiv. unreacted P–Cl per 208.5 g.	P–Cl esterified, %
45	5.42	5.18	26.62	24.85	23.77	0.02375	97.62
75	5.49	5.43	26.78	26.00	16.52	0.01652	98.35

[a] 112.5 g. of dichloridate + 96.0 methanol = 208.5 g. of reaction product.

TABLE IX

CALCULATION OF CHLORIDE ION CONCENTRATION

Time, min.	Equiv. NaOH = equiv. total acid/208.5 g.	Ml. 0.995 *N* $AgNO_3$	Ml. 0.988 *N* KCNS	Chloride ion (equiv./ 208.5 g.)
45	1.020	30.00	4.50	0.977
75	1.011	30.00	4.30	0.972

TABLE X

CALCULATION OF YIELDS FROM SOLVOLYTIC RUN

Time, min.	Total acid, equiv.	Chloride ion, equiv.	Unreacted P–Cl, equiv.	PCl + Cl ion, equiv.	>POOH,[a] equiv.	PCl(equiv.[b]) from $ArOPOCl_2$ lost as unreacted PCl and as >POOH	PCl[c] converted to P–OMe ester, %
45	1.020	0.977	0.0238	1.0008	0.0192	0.0430	95.7
75	1.011	0.972	0.0165	0.9885	0.0225	0.0390	96.1

[a] >POOH (cleavage acid) = total acid − (PCl + chloride ion), equiv. [b] Columns 4 + 6. [c] Corrected for unreacted PCl and for cleavage.

were thermostated for specified times, diluted with 5–7 ml. of carbon tetrachloride and poured into 100 ml. of water. The test-tubes were rinsed with two 5–7-ml. portions of carbon tetrachloride and the washings combined with the quench solution. The hydrogen chloride liberated was titrated with standard alkali. Control runs with the dichloridate in the absence of alcohol indicated a negligible rate of hydrolysis by water in the time involved for quenching and titration. The use of carbon tetrachloride was intended in part to prevent or reduce solubilization of unreacted dichloridate in the presence of methanol which would be expected to accelerate hydrolysis in the quench solution.

Preparation of Dimethyl *m*-Tolyl Phosphate by Solvolysis.—One-half mole (112.5 g.) of distilled *m*-tolyl phosphorodichloridate was fed over 50 minutes at 15° to 96 g. (3.0 moles) of methanol with constant stirring and external cooling. Provision was made to absorb any hydrogen chloride which evolved. Under the conditions employed, no hydrogen chloride was lost from the reaction solution. After the completion of the dichloridate feed, the reaction temperature was maintained and samples were removed with a hypodermic syringe to determine the optimum time for quenching the reaction. Approximately 5-g. aliquots were added to each of two flasks, one containing 100 ml. of dry methanol, the other 50 ml. of water–dioxane (2:3). Using the procedure described elsewhere, the two solutions were diluted after 4 hr. with 30 ml. of distilled water and titrated with standard alkali to the phenolphthalein end-point. The difference in equivalents of base consumed is equal to the equivalents P–Cl solvolyzed (Table VIII).

From the titration of the water–dioxane solution, the total acid formed was calculated. The same solutions then were titrated by the Volhard procedure for chloride ion (Table IX). The yields were calculated as shown in Table X.

The reaction product remaining after 75 minutes of "cook" time was quenched in 300 ml. of water, extracted with 55 ml. of a 10% sodium hydroxide–10% sodium chloride solution, washed twice with 50-ml. quantities of 5% sodium chloride solution, freed of water under reduced pressure, filtered and weighed. The wash waters were extracted once with benzene and the ester recovered upon drying and evaporating the latter solution was added to the main portion of the product after the last wash. The yield data are summarized in Table XI.

TABLE XI

CALCULATED AND RECOVERED YIELDS FROM SOLVOLYSIS

Time, min.	Ester yield based on titration data %	Ester yield based on titration data Wt., g.	Total yield, based on physical recovery and on 0.5 mole of dichloridate charged %	Total yield, based on physical recovery and on 0.5 mole of dichloridate charged Wt., g.
45	95.7	103.6		
75	96.2	104.0	93.2	100.9

Considering the difference between actual and calculated yields to be only 3.1 g., which easily may be attributable to handling losses, the data confirm the validity of the titration technique. As isolated in this fashion, the resulting dimethyl *m*-tolyl phosphate contained a trace of the sodium phosphate salt, approximately 0.5% calculated as $(CH_3O)(CH_3C_6H_4O)POONa$. To remove this impurity the product was distilled and yielded a heart cut of 87.2 g., b.p. 114° (1 mm.).

Anal. Calcd. for $C_9H_{13}O_4P$: C, 50.0; H, 6.02; P, 14.35. Found: C, 49.9; H, 6.1; P, 14.3.

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[CONTRIBUTION FROM THE KERCKHOFF LABORATORIES OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Isolation of a New Pteridine from *Eremothecium ashbyii* and Some Observations on its Structure[1]

BY HUGH S. FORREST AND WALTER S. MCNUTT

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A new pteridine has been isolated in crystalline form from the mold *Eremothecium ashbyii*. Investigations of its structure have shown it to have certain similarities to riboflavin, but it is probably not an intermediate in the biosynthesis of this compound.

Although it is known from experiments on the mold *Eremothecium ashbyii* that the pyrimidine portion of riboflavin arises from adenine,[2] no information is available on the intermediate steps in this process. In experiments designed to investi-

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(2) W. S. McNutt, *J. Biol. Chem.*, **219**, 365 (1956).